SILYL PHENOLS FOR PROMOTING VASCULAR HEALTH

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Applications Nos. 60/511,654, filed October 17, 2003; 60/511,663, filed October 17, 2003; 60/511,670 filed October 17, 2003; 60/537,233, filed January 20, 2004; 60/537,250, filed January 20, 2004; and 60/537,286, filed January 20, 2004, each of which is herein incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to therapeutic and prophylactic methods and compositions for improving vascular health, including methods for treating and preventing major adverse cardiac events, methods for treating and preventing vascular access dysfunction, and methods for treating and preventing male erectile dysfunction.

BACKGROUND OF THE INVENTION

Vascular health is implicated in many disease and disorder conditions and modalities. Such diseases and disorders include major adverse cardiac events, vascular access dysfunction, and male erectile dysfunction.

Major Adverse Cardiac Events

Major adverse cardiac events (MACEs), including but not limited to cardiac death, nonfatal myocardial infarction, unstable angina, stoke, or intervention procedures, such as coronary artery bypass graft surgery and percutaneous coronary intervention (PCI), are the main causes of mortality in long-term hemodialysis patients. The annual mortality rate due to MACEs in end-stage renal disease (ESRD) patients treated with hemodialysis is 10- to 20- fold higher when stratified for age (30-fold higher when not stratified) than the mortality rate due to such cardiovascular disease in the general population. Levey AS, *et al.*, "Controlling the Epidemic of Cardiovascular Disease in Chronic Renal Disease", *Report from the National Kidney foundation, Task force on cardiovascular disease,*

www.kidney.org/professionals/pysfile/cardiointro.cfm (Oct. 1998). Diabetes mellitus is also a major independent risk factor for cardiac disease and MACEs. The overall prevalence of cardiac disease is as high as 55% among adult diabetes patients.

Conventionally, treatment of dyslipidemia is the primary target for treatment and prevention of MACEs. Nonetheless, despite the enormity of this problem, there are currently no effective therapies for the treatment or prevention of major adverse cardiac events in patients suffering from end stage renal disease or diabetes. Traditional anti-atherosclerosis therapies such as statins and fibrates have been found to be largely ineffective in reducing the risk of MACEs in these patient populations. This suggests that known mechanisms of atherosclerosis and vascular occlusive disease, such as elevated low density lipoproteins (LDL), are not the primary risk factor in these populations. As such, there remains a great need for effective therapies in the treatment and prevention of MACEs.

Vascular Access Dysfunction

Vascular access dysfunction is the single most important cause of morbidity in the hemodialysis population. *United States Renal Data System: Annual Report*, Minneapolis, MN (2002). More particularly, in the end-stage renal disease (ESRD) patient population, 50% of patients treated with hemodialysis experience vascular access failure within the first year of placement, and 75% experience failure within 2 years of placement. Roy-Chaudhury *et al*, *Kidney International*, 59:2325-2334 (2001).

The most common form of vascular access procedure performed in the United States in ESRD and chronic hemodialysis patients is placement of an arteriovenous shunt. Shunt thrombosis is the cause of most vascular access dysfunction in this patient population, and in over 90% of the thrombosed grafts, the underlying pathology is a stenosis either at the venous anastomotic site or in the downstream (proximal) vein. *Id.*

Despite the enormity of this problem, there are currently no effective therapies for the treatment or prevention of vascular access dysfunction in this target population. Traditional anti-atherosclerosis therapies such as statins and fibrates have been found to be largely ineffective in treatment of the ESRD patient population. This suggests that known mechanisms of atherosclerosis and vascular dysfunction,

such as elevated low density lipoproteins (LDL), are not implicated in the proliferative and stenotic process responsible for the vascular access dysfunction observed in the ESRD patient population.

Although recent research has investigated the role of smooth muscle cells, extracellular matrix proteins, macrophages, and certain cytokines in graft stenosis, the underlying mechanisms of vascular access dysfunction in hemodialysis patients are still unclear. As such, there remains a great need for effective therapies in the treatment and prevention of vascular access dysfunction.

Erectile Dysfunction

Erectile dysfunction denotes the medical condition of inability to achieve penile erection sufficient for successful sexual intercourse. The term "impotence" is often employed to describe this prevalent condition. Erectile dysfunction may result from a variety of causes, including those secondary to clinical conditions such as hormonal insufficiency and diabetes. In addition, erectile dysfunction may arise as a side effect associated with the treatment of clinical conditions such as prostate cancer, or as a side effect related to the use of medications, alcohol, and other drugs, including for instance clomipramine or selective serotonin reuptake inhibitors (SSRI's). Approximately 140 million men worldwide, and, according to a National Institutes of Health study, about 30 million American men suffer from impotency or erectile dysfunction. It has been estimated that the latter number could rise to 47 million men by the year 2000. *See* US 20030176413A1.

The Massachusetts Male Aging Study found the combined prevalence of minimal, moderate, and complete impotence was 52% in men from ages 40 to 70 years of age. In the same study the prevalence of complete impotence increased from 5% at age 40 to 15% at age 70. *See,* H.A. Feldman *et al.*, "Impotence And Its Medical And Psychosocial Correlates: Results Of The Massachusetts Male Aging Study," *J. Urol.* 151(1): 54-61 (1994). In a more recent study, it was estimated that the prevalence of erectile dysfunction was approximately 20% in men between 50 and 59 years old. *See* C. B. Johannes, *et al.*, "Incidence of erectile dysfunction in men 40 to 69 years old: Longitudinal Results from The Massachusetts Male Aging Study," *J. Urol.* 163: 460-63 (2000). In spite of the frequent occurrence of this condition, only a small number of patients have received treatment because existing treatment

alternatives have been uniformly disagreeable (for a discussion, *see* "ABC of Sexual Health," *Brit. Med. J.* 318: 387-390 (1999)).

One of the least invasive of these treatment alternatives, vacuum pumps, entails the use of a vacuum constriction device on the penis to produce an erection. The physiology of the penis is such that blood flows in through arteries deep within the tissue while blood flows out through veins near the skin surface. By placing a plastic cylinder over the shaft of the penis and employing a vacuum pump to restrict venous blood flow from the penis, the corpus cavernosum penile tissue becomes engorged with trapped blood and an erection is produced. Common patient complaints are that this device is disruptive to the sex act, has a short duration of effectiveness, and can cause tissue damage to the penis, including outcomes such as ecchymoses of the penis. More serious tissue damage to the penis such as necrosis may occur with extended use.

Penile prosthesis implantation is an alternative treatment of erectile dysfunction, which entails surgically implanting a mechanical device inside the penis (for an example, *see* U.S. Pat. No. 5,065,744 to Zumanowshky). An implant can be a semi-rigid malleable rod or a fluid inflated tube that can be operated by the patient to achieve an erection. Although this method does not affect the ability to urinate, ejaculate, or have an orgasm, the surgery required to implant the prosthesis can lead to pain, infection, and scarring.

Recent insights into the physiological mechanism of penile erection have led to the development of other therapies for the treatment of erectile dysfunction. Studies have shown that during sexual arousal nitric oxide (NO) molecules are released from nerve endings and endothelial cells into the surrounding tissue in the penis. Nitric oxide molecules influence the enzyme guanylate cyclase to produce cyclic guanosine monophosphate (cGMP) that lowers the level of intracellular calcium and allows for the relaxation of smooth muscle cells. In the penis, the relaxation of the corpus cavernosal smooth muscle cells permits increased blood flow into the cavernosal spaces leading to a greater intracavernosal pressure and penile rigidity.

Pharmacological agents that inhibit the breakdown of cGMP may enhance or prolong penile erections during sexual stimulation. Sildenafil (VIAGRA®, Pfizer,

Inc.) is one such pharmacological agent which, when given orally, has shown success in this manner (Terrett, N. K. *et al. Bioorg. Med. Chem. Lett.* 1996, 6, 1819-1824). Sildenafil is a selective inhibitor of type V phosphodiesterase (PDE-5), a cyclic-GMP-specific phosphodiesterase isozyme (*See* R. B. Moreland et al., "Sildenafil: A Novel Inhibitor of Phosphodiesterase Type 5 in Human Corpus Cavernosum Smooth Muscle Cells," *Life Sci.*, *62*: 309-318 (1998)). Oral sildenafil is reported to be effective in about 70% of men who take it. Several additional selective PDE-5 inhibitors are in clinical trials, including UK-114542 (Pfizer), IC-351 (ICOS Corp.), M-54033 and M-54018 (Mochida Pharmaceutical Co.), and E-4010 (Eisai Co., Ltd.).

Other pharmacological approaches to the treatment of erectile dysfunction have been described (*see, e.g.*, "Latest Findings on the Diagnosis and Treatment of Erectile Dysfunction," *Drug News & Perspect.*, 9: 572-575 (1996); "Oral Pharmacotherapy in Erectile Dysfunction," *Cur. Opin. in Urology*, 7: 349-353 (1997)). For example, a product under clinical development by Zonagen is an oral formulation of the alpha-adrenoceptor antagonist phentolamine mesylate under the brand name of Vasomax®.

SUMMARY OF THE INVENTION

The present invention generally relates to the therapeutic and prophylactic methods and compositions for improving vascular health. In one embodiment, methods are provided comprising administering a therapeutically or prophylactically effective amount of at least one compound of the present invention to a subject in need of treatment, wherein the said amount is therapeutically or prophylactically effective in the treatment or prevention of major adverse cardiac events, vascular access dysfunction, or male erectile dysfunction.

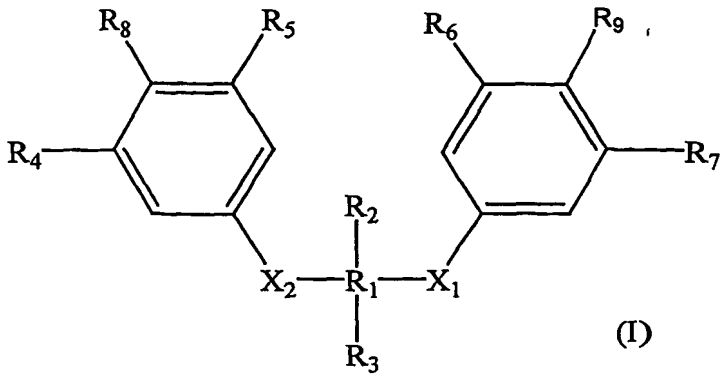
More particularly, in one another aspect, the invention is directed to methods for the prophylactic or therapeutic treatment of major adverse cardiac events (MACEs). particularly in patients with an increased oxidative burden or elevated oxidative stress, such as hemodialysis, ESRD, and diabetic patients. The methods of the invention are particularly suited for the therapeutic treatment and prevention of major adverse cardiac events in hemodialysis, ESRD, and diabetic patients. Additionally, the methods of the present invention are effective in the prophylactic or

therapeutic treatment of major adverse cardiac events without detrimental side effects such as suppression of high density lipoprotein (HDL) cholesterol levels or QTc interval prolongation.

In another aspect, the invention relates to prophylactic or therapeutic treatment of vascular access dysfunction, particularly in patients who are refractory to statin and/or fibrate treatment, for example, those suffering from ESRD. The methods of the present invention are particularly suited for the treatment and prevention of arteriovenous shunt stenosis in subjects receiving hemodialysis. Additionally, the methods of the present invention are effective in the prophylactic or therapeutic treatment of vascular access dysfunction without detrimental side effects such as suppression of high density lipoprotein (HDL) cholesterol levels or QTc interval prolongation.

In yet another aspect, the invention relates to the prophylactic or therapeutic treatment of erectile dysfunction in male patients. Impaired neurogenic and endothelium dependent relaxation of the penile artery and the corpus cavernosum are associated with conditions involving vascular dysfunction, such as diabetes. Multiple mechanisms have been implicated in the vascular dysfunction associated with diabetes, including an excessive generation of reactive oxygen species which leads to the quenching of nitric oxide (NO) released by the endothelium and nitrergic nerves, and increased oxidative stress in vascular tissues. The methods and compositions of this invention are directed to limiting the deleterious effects of the mechanisms implicated in erectile dysfunction, particularly erectile dysfunction associated with diabetes.

In one embodiment, the methods of the invention comprise administering to a subject in need of treatment, *e.g.*, a subject having an increased oxidative burden or elevated oxidative stress and thus at risk of major adverse cardiac events, a subject having a vascular access shunt or graft, or a subject suffering from diabetes and experiencing erectile dysfunction or seeking prophylactic therapy, an amount of a compound of Formula (I) which is therapeutically or prophylactically effective in said treatment:



(I)

wherein

X_1 and X_2 are independently selected from the group consisting of oxy and a dialkyl substituted silyl;

R_1 is alkyl; R_2 and R_3 are independently selected from the group consisting of H and an alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl,–O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, and –CO-(alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, or –CO-(alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of: C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, alkyl-substituted amino, $–NO_2$, –CN, –NC, $–C(=NH)(-NH_2)$ (*i.e.*, amidine), –SH, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

In a preferred embodiment, the methods comprise administering to a subject in need of treatment, a compound of Formula (I) wherein:

X_1 and X_2 are independently selected from the group consisting of oxy and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

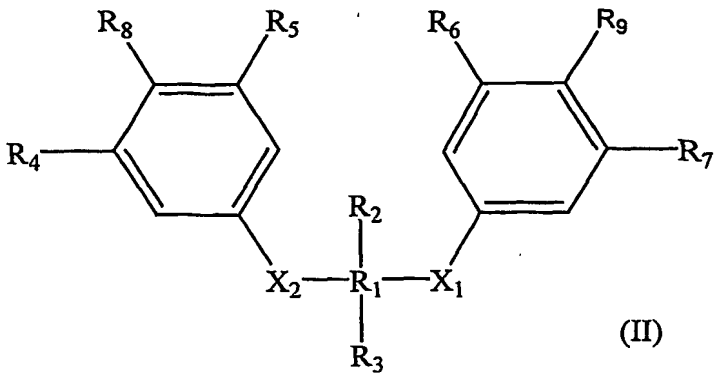
R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain C_1-C_6 alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl,–O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, or –CO-(C_2-C_6 alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, –OCH_3, –OCH_2CH_3, halomethyl, dihalomethyl, trihalomethyl, –NH_2, alkyl-substituted amino, –NO_2, –CN, –NC, –C(=NH)(-NH_2) (*i.e.*, amidine), –SH, –COOH, –$COOCH_3$, and $COOCH_2CH_3$.

In another embodiment, the methods of the invention comprise administering to a subject in need of treatment, *e.g.*, a subject having an increased oxidative burden or elevated oxidative stress and thus at risk of major adverse cardiac events, a subject having a vascular access shunt or graft, or a subject suffering from diabetes and experiencing erectile dysfunction or seeking prophylactic therapy, an amount of a compound of Formula (II) which is therapeutically or prophylactically effective in said treatment:



(II)

wherein

X_1 and X_2 are independently selected from the group consisting of thio, oxy, and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl,–O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, and –CO-(alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, and –CO-(alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, alkyl-substituted amino. $–NO_2$, –CN, –NC, $–C(=NH)(-NH_2)$ (*i.e.*, amidine),

–SH, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

In a preferred embodiment, the methods comprise administering to a subject in need of treatment, a compound of Formula (II) wherein:

X_1 and X_2 are independently selected from the group consisting of thio, oxy, and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

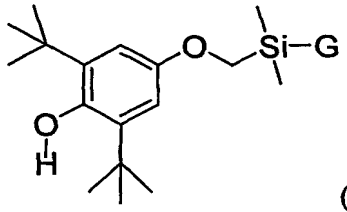
R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain C_1-C_6 alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH;

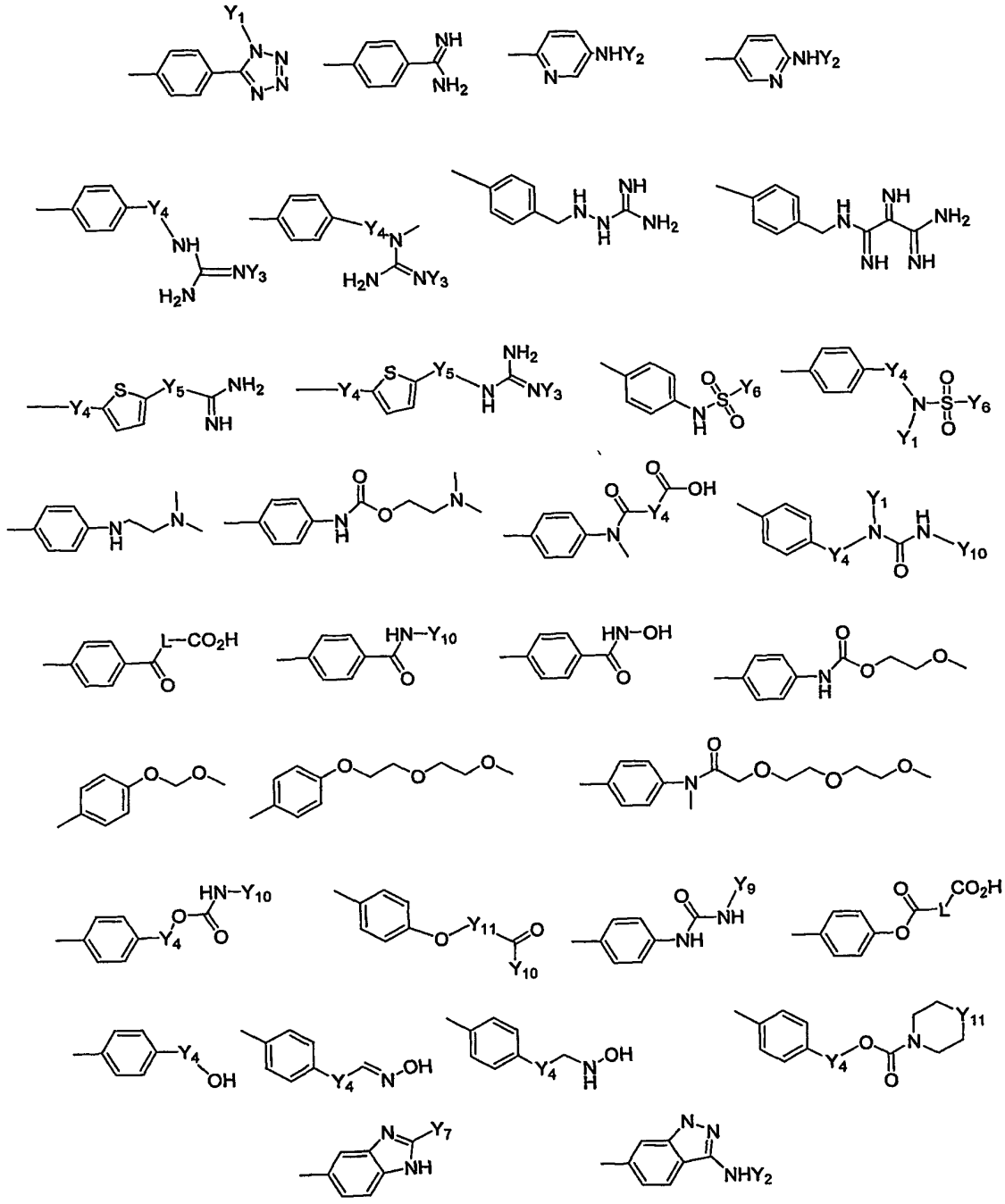
wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, alkyl-substituted amino, $–NO_2$, –CN, –NC, –C(=NH)($-NH_2$) (*i.e.*, amidine), –SH, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

In yet another embodiment, methods are provided comprising administering to a subject in need of treatment, *e.g.*, a subject having an increased oxidative burden or elevated oxidative stress and thus at risk of major adverse cardiac events, a subject having a vascular access shunt or graft, or a subject suffering from diabetes and experiencing erectile dysfunction or seeking prophylactic therapy, an amount of a compound of Formula (V) which is therapeutically or prophylactically effective in said treatment:



(V)

wherein G is selected from the group consisting of:



wherein:

Y_1 is –H, C_1-C_4 alkyl, or C_3-C_6 alkenyl;

Y_2 is –H, C_1-C_4 alkyl, or C_3-C_6 alkenyl, aryl, heteroaryl, aryloyl, alkanoyl, or heteroaryloyl;

Y_3 is –H, –CN, C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl or heteroaryl;

Y_4 is $(CH_2)_n$, where n is 0-4, or C_3-C_6 alkenyl;

Y_5 is NH, $(CH_2)_n$, where n is 0-4, or C_2-C_6 alkenyl;

Y_6 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_7 is H, C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or NH-Y_8;

Y_8 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_9 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, or heteroaryl;

Y_{10} is H, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_{11} is C_1-C_4 alkyl, C_3-C_6 alkenyl, -O-, or -N-(Y_1);

L is C_1-C_6 alkyl or C_2-C_6 alkenyl; and

wherein G may be additionally substituted with one or more substituents independently selected from the group consisting of –F, –Cl, –Br, –I, $–NH_2$, alkyl-substituted amino, –OH, –CN, –SH, $–CH_3$, $–CH_2CH_3$, $–CF_3$, $–OCH_3$, $–OCH_2CH_3$, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

In another aspect of the invention, compounds of the present invention, in particular compounds of Formula V, useful in the methods of the invention are provided, as well as metabolites of such compounds and pharmaceutical compositions comprising such compounds.

Aspects of the invention will be apparent to one of skill in the art based on the following figures and detailed description.

In another aspect of the invention, compounds of the present invention, in particular compounds of Formula V, useful in the methods of the invention are provided, as well as metabolites of such compounds and pharmaceutical compositions comprising such compounds.

Aspects of the invention will be apparent to one of skill in the art based on the following figures and detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the antioxidant activity *ex vivo* following oral administration of a t-butyl phenol compound of the invention: copper-induced

oxidation of serum isolated from rabbits fed a 0.5% cholesterol/10% corn oil diet for 70 days.

Figure 2 illustrates the inhibition of cytokine-induced VCAM-1 expression in human coronary artery smooth muscle cells (CASMC) and in human umbilical vein endothelial cells (HUVEC) by a t-butyl phenol compound of the invention as compared with probucol.

Figure 3 illustrates changes in total peripheral conductance (TPC) in response to intravenous carbachol (1, 5, 10, 20 mg/kg) in control group rabbits and test group rabbits treated with a t-butyl phenol compound of the invention (300 mg/day for 70 days).

Figure 4 illustrates endothelial cell NO activity as a function of t-butyl phenol compound and TNF-α.

Figure 5 illustrates inducement of HMOX-1 expression by a t-butyl phenol compound of the invention in unstimulated whole blood.

Figure 6 illustrates inducement of HMOX-1 expression by a t-butyl phenol compound of the invention in LPS stimulated whole blood.

Figure 7 illustrates (a) quantitative morphometry and (b) intimal-to-medial ratio in a model of mechanical injury in Apo $E^{-/-}$ male mice that were treated with placebo or a representative compound of the invention and fed a high fat diet supplemented with 1.25% cholesterol for 12 weeks prior to injury.

Figure 8 illustrates percent CD45 positive cells (number of immunostained positive cells for CD45/total number of nuclei) in neointima and media of carotid arteries in a model of mechanical injury in Apo $E^{-/-}$ male mice that were treated with placebo or a representative compound of the invention and were fed a high fat diet supplemented with 1.25% cholesterol for 12 weeks prior to injury.

Figure 9 illustrates percent Brdu positive cells (number of immunostained positive cells for Brdu/total number of nuclei) in neointima and media of carotid arteries in a model of mechanical injury in Apo $E^{-/-}$ male mice that were treated with placebo or a representative compound of the invention and were fed a high fat diet supplemented with 1.25% cholesterol for 12 weeks prior to injury.

Figure 10 illustrates a time course of blood glucose levels in diabetic rats and 8 week streptozotocin-induced diabetic rats treated or untreated with a representative

compound of the invention (0.3% in rat chow). Morning blood glucose levels are determined employing tail vein blood samples obtained from conscious rats. Data are expressed as the mean ± SEM (standard error of the mean). The number of animals employed is indicated by n. Blood glucose levels are significantly increased in diabetic animals. No significant differences are observed between treated and untreated diabetic animals.

Figure 11 illustrates a time course of blood glucose levels in non-diabetic rats, 12 week streptozotocin-induced untreated diabetic rats, and diabetic rats untreated for 8 weeks and then treated with a representative compound of the invention (0.3% in rat chow) for 4 additional weeks. Morning blood glucose levels are determined employing tail vein blood samples obtained from conscious rats. Data are expressed as the mean ± SEM. The number of animals employed is indicated by n. Blood glucose levels are significantly increased in diabetic animals. No significant differences are observed between treated and untreated diabetic animals.

Figure 12 illustrates mean arterial pressure (MAP) values in panel A, and heart rate (HR) in panel B of non-diabetic rats and 8 week streptozotocin-induced diabetic rats treated or untreated with a representative compound of the invention (0.3% in rat chow). MAP and HR were determined in anesthetized rats before evaluation of erectile responses to cavernosal nerve stimulation. Data are expressed as the mean ± SEM. The number of animals employed is indicated by n. ***$p < 0.005$ vs. no diabetes by one way ANOVA followed by a Student-Newman-Keuls post hoc test.

Figure 13 illustrates effect of preventative treatment with a representative compound of the invention (0.3% in rat chow) on erectile responses in anesthetized 8 week streptozotocin-induced diabetic male rats. Data are expressed as the mean ± SEM of the area under the curve (mm Hg x seconds) of intracavernosal pressure (ICP) increase to cavernosal nerve electrical stimulation normalized by MAP values at the time of each stimulation. ***$p < 0.005$ vs. frequency-response curve in untreated diabetic rats by two-factors ANOVA test.

Figure 14 illustrates effect of preventative treatment with a representative compound of the invention (0.3% in rat chow) on erectile responses in anesthetized 8 week streptozotocin-induced diabetic male rats. Data are expressed as the mean ± SEM of the peak increment (mm Hg) of ICP increase to cavernosal nerve electrical

stimulation normalized by MAP values at the time of each stimulation. ***p < 0.005 vs. frequency-response curve in untreated diabetic rats by two-factors ANOVA test.

Figure 15 illustrates mean arterial pressure (MAP) values (left panel) and the heart rate (HR) levels (right panel) of non-diabetic rats, 12 weeks streptozotocin-induced untreated diabetic rats, and diabetic rats untreated for 8 weeks and then treated with a representative compound of the invention (0.3% in rat chow) for 4 additional weeks. MAP and HR were determined in anesthetized rats before evaluation of erectile responses to cavernosal nerve stimulation. Data are expressed as the mean ± SEM. The number of animals employed is indicated by n. ***p < 0.005 vs. no diabetes by one way ANOVA followed by a Student-Newman-Keuls post hoc test.

Figure 16 illustrates erectile responses in anesthetized 12 weeks streptozotocin-induced untreated diabetic male rats, and diabetic rats untreated for 8 weeks and then treated with a representative compound of the invention (0.3% in rat chow) for 4 additional weeks. Data are expressed as the mean ± SEM of the area under the curve (mm Hg x seconds) of ICP increase to cavernosal nerve electrical stimulation normalized by MAP values at the time of each stimulation. **p < 0.01 vs. frequency-response curve in untreated diabetic rats by two-factors ANOVA test.

Figure 17 illustrates erectile responses in anesthetized 12 weeks streptozotocin-induced untreated diabetic male rats, and diabetic rats untreated for 8 weeks and then treated with a representative compound of the invention (0.3% in rat chow) for 4 additional weeks. Data are expressed as the mean ± SEM of the peak increment (mm Hg) of ICP increase to cavernosal nerve electrical stimulation normalized by MAP values at the time of each stimulation. **p < 0.01 vs. frequency-response curve in untreated diabetic rats by two-factors ANOVA test.

DETAILED DESCRIPTION OF THE INVENTION

The present invention generally relates to therapeutic and prophylactic methods and compositions for improving vascular health. In accordance with the present invention, factors that contribute to vascular health may include, but are not limited to: reducing the expression of VCAM-1; preventing the loss of NO activity caused by TNF-α, quenching by ROS, or by inflammation and inflammatory

cytokines; inducing the expression of heme oxygenase-1 (HMOX-1); reducing neointima thickening and intimal-to-medial ratios following vascular injury; or inhibiting leukocyte recruitment to the site of vascular injury or distress. Disease states and conditions implicated by such vascular health factors include major adverse cardiac events, vascular access dysfunction, and male erectile dysfunction.

More particularly, major adverse cardiac events (MACEs) are the main causes of mortality in long-term hemodialysis patients, such as those suffering from ESRD. Diabetes mellitus is also a major independent risk factor for cardiac disease and MACEs. While atherosclerosis contributes to underlying pathologic mechanisms of the occurrence of MACEs in these patients, additional risk factors play a significant role. This is supported by the fact that the risk of occurrence of MACEs in the hemodialysis, ESRD, and diabetic patient populations is largely unaffected by traditional anti-atherosclerosis therapies such as statins and fibrates. Moreover, conventional lipid risk factors such as LDL cholesterol do not adequately explain the overwhelming occurrence of MACEs observed in these patient populations.

Another leading cause of morbidity and hospitalization in the hemodialysis population, particularly ESRD patients, is vascular access dysfunction. Vascular access dysfunction or stenosis is a fundamentally different disorder than atherosclerosis, and, depending on the graft, can be characterized by very different vascular flow dynamics (*e.g.*, an arterial to venous shunt links a high pressure blood flow from an arterial source to a typically low pressure venous source). While atherosclerosis and vascular access dysfunction may share certain underlying pathologic mechanisms, such as inflammatory responses, they are not mediated in the same physical context (*e.g.*, inflammatory responses in a vascular access graft or shunt is different from the inflammatory responses that occur in an atherosclerotic plaque). This is again supported by the fact that vascular access dysfunction in the hemodialysis patient population is largely unaffected by traditional anti-atherosclerosis therapies such as statins and fibrates. Moreover, conventional lipid risk factors such as LDL cholesterol do not adequately explain the overwhelming occurrence of vascular access dysfunction observed in the hemodialysis patient population.

Current research does suggest that hemodialysis patients are exposed to increased oxidative stress with decreased lipoprotein resistance to oxidation, have higher levels of plasma VCAM-1, indicating vascular inflammation, have decreased endothelium-dependent vasodilation, and have low NO production, compared to controls. Annuk *et al.*, *J Am Soc Nephrol*, 12:2747-2752 (2001); Bolton *et al.*, *Nephrol Dial Transplant*, 16:1189-1197 (2001); Schmidt et al., *Kidney Int*, 58:1261-1266 (2000). In atherosclerotic vessels, it has been suggested that the heme oxygenase – carbon monoxide signaling pathway plays a physiological role in the maintenance of vascular tone and health in atherosclerotic vessels. Siow, *et al.*, *Cardiovascular Res.*, 41:385-94 (1999).

While atherosclerosis is a contributing factor to the prevalence of MACEs in hemodialysis, ESRD, and diabetic patients, without being limited by theory, according to the present invention, the above discussed non-LDL cholesterol related mechanisms are believed to contribute substantially to the occurrence of MACE in this patient population. Further, vascular access dysfunction and stenosis are different from atherosclerosis, and without being limited by theory, according to the present invention, the above-discussed non-LDL cholesterol related mechanisms are also believed to contribute substantially to vascular access dysfunction in the ESRD patient population.

As such, in one aspect of the invention, compounds and pharmaceutical compositions having specific pharmacological properties that target these mechanisms have been identified for use in conjunction with the methods of the invention. More particularly, the compounds disclosed herein have been shown to target these non-LDL cholesterol related mechanisms, thereby offering a novel approach for the treatment, prevention and reduction of the risk occurrence of MACEs and/or vascular access dysfunction in patients with an increased oxidative burden or elevated oxidative stress, such as hemodialysis, ESRD, and diabetic patients.

In another aspect of the invention, the compounds and methods of the present invention provide a safe, effective, and convenient method of treating erectile dysfunction secondary to conditions such as diabetes. The compounds may be administered in conjunction with other active agents or devices known to increase the erectile response to achieve additive or synergistic effects. Current research indicates

that erectile dysfunction secondary to a variety of conditions may be treated through the use of drugs directly affecting signaling pathways that lead to relaxation of the smooth muscle cells of the penis, thereby permitting it to become engorged with arterial blood and giving rise to an erectile response. The most notable compound to be employed in the treatment of erectile dysfunction is sildenafil, sold under the trade name VIAGRA®. Sildenfil and other PDE-5 inhibitors act through the inhibition of cGMP degradation.

"Major adverse cardiac events" or "MACEs," as used herein, includes cardiac death, nonfatal myocardial infarction, unstable angina, stoke, or intervention procedures, such as coronary artery bypass graft surgery and percutaneous coronary intervention (PCI), but is not limited to such, as one of ordinary skill will recognize.

"Vascular access" for hemodialysis, as used herein, means any in-line or arterial-to-venous connection used during hemodialysis, whether a natural or artificial device. A "shunt" in this context generally means a prosthetic vascular access graft or device made of natural or artificial (*e.g.*, often PTFE) material. "Vascular access dysfunction" refers to any defect that impairs the ability of the graft or device to function properly during dialysis or that increases the risk of morbidity to the patient, including but not limited to narrowing, stenosis, occlusion, weakening, susceptibility to clot formation or infection, pain or discomfort for the patient, etc.

"Erectile dysfunction" as used herein, means an inability to obtain an erection of sufficient rigidity, duration, or sufficient rigidity and duration. Measures of sufficient rigidity and duration are those required to achieve penile erection sufficient for successful sexual intercourse.

A. Methods of the Invention

In one aspect, the invention is directed to methods for the prophylactic or therapeutic treatment of major adverse cardiac events (MACEs), particularly in patients with an increased oxidative burden or elevated oxidative stress, such as hemodialysis, ESRD, and diabetic patients. The methods of the invention are particularly suited for the therapeutic treatment and prevention of major adverse cardiac events in hemodialysis, ESRD, and diabetic patients. Additionally, the methods of the present invention are effective in the prophylactic or therapeutic treatment of major adverse cardiac events without detrimental side effects such as

suppression of high density lipoprotein (HDL) cholesterol levels or QTc interval prolongation.

Such methods of the invention generally comprise administering a therapeutically or prophylactically effective amount of at least one compound of the present invention to a subject in need of treatment for major adverse cardiac events or at risk of developing such (especially those having an increased oxidative burden or elevated oxidative stress, such as hemodialysis, ESRD, and diabetic patients). Without intending to be limited by theory, it is believed that the methods of the present invention act through a combination of mechanisms possibly including decreasing the expression of VCAM-1; prevention of the loss of NO activity caused by TNF-α or quenching by ROS; inducing the expression of heme oxygenase-1 (HMOX-1), reducing neointima thickening and intimal-to-medial ratios following vascular injury; and inhibiting leukocyte recruitment to the site of vascular injury.

In another embodiment, such methods of the invention comprise identifying a subject with increased oxidative burden or elevated oxidative stress, and administering a compound of the invention to said subject. The skilled clinician will understand methodologies for determining oxidative burden and stress levels. In the methods of the invention, the subject may optionally have normal or normalized lipid levels (*i.e.*, lipid levels normalized through conventional medications, diet, and/or exercise).

In another aspect, the invention is directed to methods for the treatment and prevention of vascular access dysfunction, particularly in patients such as those suffering from ESRD or who are refractory to statin and/or fibrate treatment. The methods of the invention are particularly suited for the treatment and prevention of arteriovenous shunt stenosis in subjects receiving hemodialysis. Additionally, the methods of the present invention are effective in the prophylaxis or treatment of vascular access dysfunction without detrimental side effects such as suppression of high density lipoprotein (HDL) cholesterol levels or QTc interval prolongation.

Such methods of the invention generally comprise administering a therapeutically or prophylactically effective amount of at least one compound of the present invention to a subject in need of treatment for vascular access dysfunction or at risk of developing vascular access dysfunction (*e.g.*, anyone having vascular access

for hemodialysis, or especially those having a prior history of vascular access dysfunction, stenosis, or occlusion). Without intending to be limited by theory, it is believed that the methods of the present invention act through a combination of mechanisms possibly including decreasing the expression of VCAM-1; prevention of the loss of NO activity caused by TNF-α; inducing the expression of heme oxygenase-1 (HMOX-1), reducing neointima thickening and intimal-to-medial ratios following vascular injury; and inhibiting leukocyte recruitment to the site of vascular injury.

In yet another aspect, the invention is directed to methods for the preventative and therapeutic treatment of erectile dysfunction, particularly in patients such as those suffering from diabetes. The methods of the invention are particularly suited for the preventative and therapeutic treatment of erectile dysfunction as a result of being convenient, effective, painless and discreet. The mechanism of action associated with the methods of the present invention are distinct from known treatments such as PDE-5 inhibitors, and are also safe and free from the potential of tissue damage associated with use of devices such as vacuum constriction devices. In addition, the methods of the present invention avoid risks associated with surgical penile prosthesis implantation.

The methods of the invention generally comprise administering a therapeutically or prophylactically effective amount of at least one compound of the present invention to a subject in need of treatment for erectile dysfunction or at risk of developing erectile dysfunction (*e.g.*, individuals suffering from diabetes). Without intending to be limited by theory, it is believed that the methods of the present invention act through a combination of mechanisms that promote vascular health, possibly including reducing the expression of VCAM-1; preventing the loss of NO activity caused by TNF-α, quenching by ROS, or by inflammation and inflammatory cytokines; inducing the expression of heme oxygenase-1 (HMOX-1); and inhibiting leukocyte recruitment to the site of vascular injury or distress.

In one embodiment, methods are provided comprising administering a therapeutically or prophylactically effective amount of at least one compound of the present invention to a subject in need of treatment, wherein the said amount is

therapeutically or prophylactically effective in the treatment or prevention of major adverse cardiac events, vascular access dysfunction, or male erectile dysfunction.

The compound(s) of the present invention may be administered to the subject *via* any drug delivery route known in the art. Specific exemplary administration routes include oral, ocular, vaginal, rectal, buccal, topical, nasal, ophthalmic, subcutaneous, intramuscular, intraveneous (bolus and infusion), intracerebral, transdermal, and pulmonary. A preferred formulation for administering such a compound is described in International Application No. [Serial Number Pending], entitled Self-Emulsifying Drug Delivery Systems for Hydrophobic Therapeutic Compounds, attorney docket no. 18528.737, which is incorporated herein by reference.

In one embodiment, the compound(s) of the present invention are administered in a prophylactically effective amount following a determination of an increased risk of occurrence of MACEs due to an increased oxidative burden or elevated oxidative stress, as determined by a skilled clinician. In another embodiment, the compound(s) of the present invention are administered in a therapeutically effective amount upon first indication of a MACE, for example mycardial infarction or percutaneous coronary intervention (PCI) procedure.

In another embodiment, the compound(s) of the present invention may be administered at any time immediately preceding, concurrently with, or subsequent to placement of the vascular access device, as determined by the skilled clinician. For example, it may be desired to pre-treat a patient prior to installation of a vascular access device for a period of one day to one month or longer, in order to reduce any existing local inflammation at the site of the vascular access graft or device. It is further contemplated that ongoing or chronic prophylactic treatment could begin as early as initial shunt placement to prevent or reduce occurrence of graft/shunt stenosis. Alternatively, treatment may begin at any point on the continuum of shunt stenosis or dysfunction. More particularly, in one embodiment, the compound(s) of the present invention are administered in a prophylactically effective amount immediately following initiation of hemodialysis (or other vascular access event). In another embodiment, the compound(s) of the present invention are administered in a

therapeutically effective amount upon first indication of vascular access dysfunction, for example stenosis, occlusion, or failure.

In yet another embodiment, the compound(s) of the present invention may be administered prophylactically to individuals deemed to be at risk, such as patients suffering from cardiovascular disease or conditions associated with vascular dysfunction such as diabetes, at any time preceding the onset of erectile dysfunction symptoms. Prophylactic treatment may in fact begin concurrently with the diagnosis and treatment of conditions deemed to place an individual at risk of suffering from erectile dysfunction. In the alternative, it is possible to treat individuals subsequent to occurrence of erectile dysfunction symptoms, either to ameliorate the condition, or to prevent or reduce further loss of the ability to achieve and sustain an erection. More particularly, in one embodiment, the compound(s) of the present invention are administered to an individual at risk of developing erectile dysfunction in a prophylactically effective amount prior to the onset of symptoms. In another embodiment, the compound(s) of the present invention are administered in a therapeutically effective amount upon first indication of erectile dysfunction, for example upon early occurrences of the inability by a diabetic to maintain a penile erection.

The terms therapeutically or prophylactically effective amount, as used herein, refer to an amount of a pharmaceutical agent to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic or preventative effect, including a reduction in risk of occurrence. The effect can be detected by, for example, chemical markers, antigen levels, or time to a measurable event, such as a MACE, shunt stenosis or failure, or the duration of an erection or intracavernosal pressure. Therapeutic effects also include reduction in physical symptoms, such as vascular inflammation. The precise effective amount for a subject will depend upon the subject's weight, size, and health, the nature and extent of the condition, and the therapeutics or combination of therapeutics selected for administration. Therapeutically or prophylactically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgement of the clinician.

For any compound, the therapeutically or prophylactically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio, ED_{50}/LD_{50}. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies may be used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

More specifically, the concentration-biological effect relationships observed with regard to the compound(s) of the present invention indicate an initial target plasma concentration ranging from approximately 5 μg/mL to approximately 100 μg/mL, from approximately 10 μg/mL to approximately 50 μg/mL, or from approximately 10 μg/mL to approximately 25 μg/mL. To achieve such plasma concentrations, the compounds of the invention may be administered at doses that vary from 0.1 μg to 100,000 mg, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. However, in general the dose will be in the range of about 1mg/day to about 10g/day, or about 0.1g to about 3g/day, or about 0.3g to about 3g/day, or about 0.5g to about 2g/day, in single, divided, or continuous doses for a patient weighing between about 50 to about 100 kg (dose may be adjusted for patients above or below this weight range).

The exact dosage will be determined by the practitioner, in light of factors related to the subject that requires treatment. Dosage and administration are adjusted

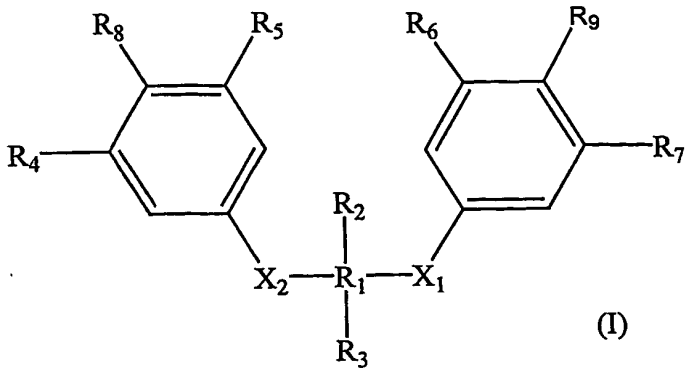
to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include, for example, the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

B. Compounds of the Invention

In another aspect of the invention, compounds useful in the prophylaxis or treatment of MACEs, vascular access dysfunction, or male erectile dysfunction are provided. The compounds of the invention are generally t-butyl phenol compounds that are effective in the prophylaxis or therapeutic treatment of MACEs, vascular access dysfunction, or male erectile dysfunction, preferably without detrimental side effects such as suppression of HDL cholesterol levels or QTc interval prolongation.

The compounds of the present invention appear to target multiple biochemical mechanisms relevant to the treatment of vascular disorders, and may be employed to treat, or prophylactically to prevent or reduce the risk of occurrence of MACE, vascular dysfunction resulting from the placement of a vascular access device, or male erectile dysfunction particularly in patients with an increased oxidative burden or elevated oxidative stress. More particularly, the compounds of the present invention are particularly useful in the treatment of hemodialysis, ESRD, and diabetic patients.

The compounds of the invention are structurally related to probucol, 2,[3]-tert-butyl hydroxyanisole (BHA), 2,6-di-tert-butyl methylphenol (BHT), and other 2,6-di-alkyl phenols known in the art. Preferred compounds of the present invention useful in the methods of the invention include those of Formula (I) shown below:



(I)

wherein

X_1 and X_2 are independently selected from the group consisting of oxy and a dialkyl substituted silyl;

R_1 is alkyl; R_2 and R_3 are independently selected from the group consisting of H and an alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl,–O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, and –CO-(alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, or –CO-(alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of: C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, alkyl-substituted amino, $–NO_2$, –CN, –NC, –C(=NH)($-NH_2$) (*i.e.*, amidine), –SH, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

In one embodiment, the methods comprise administering to a subject in need of treatment, a compound of Formula (I) wherein:

X_1 and X_2 are independently selected from the group consisting of oxy and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

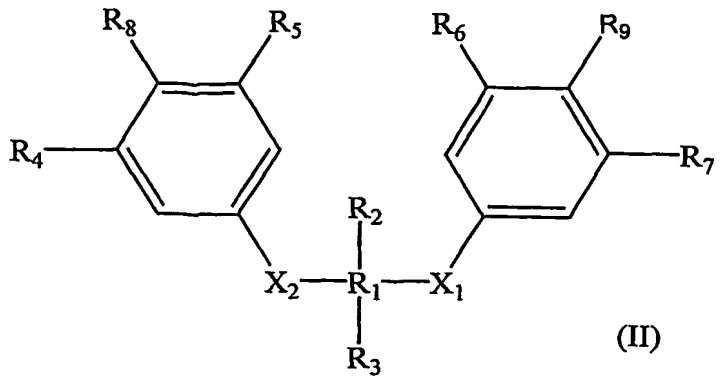
R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain C_1-C_6 alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl,–O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, or –CO-(C_2-C_6 alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, alkyl-substituted amino, $–NO_2$, –CN, –NC, –C(=NH)($-NH_2$) (*i.e.*, amidine), –SH, –COOH, $–COOCH_3$, and $COOCH_2CH_3$.

Particular compounds of Formula (I) include those wherein R_4 and R_5 are tert-butyl, and R_8 is hydroxy. Further compounds of Formula (I) are those wherein X_1 and X_2 are independently selected from the group consisting of oxy and dimethyl-silyl; R_1 is methylene; R_2 and R_3 are hydrogen, R_4, R_5, R_6, and R_7 are independently selected from the group consisting of hydrogen and tert-butyl; and R_8 and R_9 are independently selected from the group consisting of hydroxy and methoxy.

In another embodiment, the compounds of the present invention include those of Formula (II), as shown below.



(II)

wherein

X_1 and X_2 are independently selected from the group consisting of thio, oxy, and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl,–O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, and –CO-(alkenyl)-COOH;

wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(alkyl), –OCO-(H or alkyl), –OCO-(alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(alkyl)-COOH, –(alkenyl)-COOH, –OCO-(alkyl)-COOH, –OCO-(alkenyl)-COOH, –CO-(alkyl)-COOH, and –CO-(alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, alkyl-substituted amino. $–NO_2$, –CN, –NC, $–C(=NH)(-NH_2)$ (*i.e.*, amidine),

–SH, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

In one embodiment, the methods comprise administering to a subject in need of treatment, a compound of Formula (II) wherein:

X_1 and X_2 are independently selected from the group consisting of thio, oxy, and a dialkyl substituted silyl;

R_1 is C_1-C_4 alkyl;

R_2 and R_3 are independently selected from the group consisting of H and a C_1-C_4 alkyl;

R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, methoxy, and a branched or straight chain C_1-C_6 alkyl; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, trifluoromethyl, halide, amine, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH;

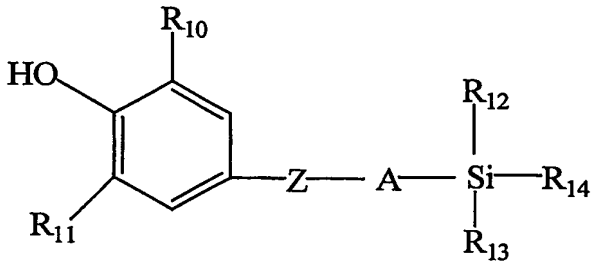
wherein when the R_8 or R_9 substituents are alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, –O(C_1-C_6 alkyl), –OCO-(H or C_1-C_7 alkyl), –OCO-(C_3-C_7 alkenyl), –OCO-(aryl), –OCO-(heteroaryl), –(C_0-C_8 alkyl)-COOH, –(C_2-C_8 alkenyl)-COOH, –OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_2-C_6 alkenyl)-COOH, –CO-(C_0-C_6 alkyl)-COOH, and –CO-(C_2-C_6 alkenyl)-COOH, they may be independently substituted with one or more functionalities independently selected from the group consisting of C_1-C_6 alkyl, halogen, –OH, $–OCH_3$, $–OCH_2CH_3$, halomethyl, dihalomethyl, trihalomethyl, $–NH_2$, alkyl-substituted amino, $–NO_2$, –CN, –NC, –C(=NH)($–NH_2$) (*i.e.*, amidine), –SH, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

Again, particular compounds are those wherein R_4 and R_5 are tert-butyl, and R_8 is hydroxy. More particularly preferred compounds of Formula (II) include those wherein X_1 and X_2 are thio; R_1 is methylene; R_2 and R_3 are methyl; R_4, R_5, R_6, and R_7 are tert-butyl; R_8 is hydroxy; and R_9 is butandioate (*i.e.*, succinic acid mono-{2,6-di-tert-butyl-4-[1-(3,5-di-tert-butyl-4-hydroxy-phenylsulfanyl)-1-methyl-ethylsulfanyl]-phenyl} ester).

Other embodiments include those wherein X_1 and X_2 are independently selected from the group consisting of thio and dimethyl-silyl; R_1 is methylene; R_2 and R_3 are independently selected from the group consisting of hydrogen and methyl; R_4, R_5, R_6, and R_7 are independently selected from the group consisting of hydrogen and

tert-butyl; and R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, methoxy, and butandioate; with the proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both hydroxy.

In another aspect of the invention, compounds useful in the methods of the present invention include one or more of a variety of phenolic antioxidants having Formula (III), shown below. Such phenolic compounds are disclosed in U.S. Patent Nos. 5,155,250; 5,532,400; 5,962,435; and 5,677,291, the entireties of which are herein incorporated by reference. Specifically, the phenolic anitoxidants include those 2,6-di-alkyl-4-silyl-phenols having the general Formula (III).



(III)

wherein: R_{10}, R_{11}, R_{12} and R_{13} are each independently a C_1 - C_6 alkyl group;

Z is a thio, oxy or methylene group;

A is a C_1 - C_4 alkylene group; and

R_{14} is a C_1 - C_6 alkyl or $-(CH_2)_n-(Ar)$

wherein n is an integer 0, 1, 2 or 3; and Ar is phenyl or napthyl unsubstituted or substituted with one to three substituents selected from the group consisting of hydroxy, methoxy, ethoxy, chloro, fluoro or C_1 - C_6 alkyl group.

Compounds of Formula (III) can be prepared by methods known to those in the art, and particularly by the methods disclosed in U.S. Patent No. 5,155,250, particularly col. 3, line 12 through col. 8, line 44. Such compounds preferably have vascular protective properties, for example, or other therapeutic uses where antioxidant properties are desirable.

Specific examples of 2,6-di-alkyl-4-silyl-phenols include without limitation:

2,6-di-t-butyl-4[(triethylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(diethylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{diethyl-(4-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{diethyl-(2-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[(tripropylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(dipropylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{dipropyl(4-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{dipropyl(2-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[(triisopropylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(diisopropylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{diisopropyl-(4-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{diisopropyl-(2-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[(tributylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(dibutylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{dibutyl-(4-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{dibutyl-(2-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[(triisobutylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(diisobutylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{diisobutyl-(4-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{diisobutyl-(2-methoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[(tri-t-butylsilyl)methylthio]phenol

2,6-di-t-butyl-4[(di-t-butylphenylsilyl)methylthio]phenol

2,6-di-t-butyl-4[{di-t-butyl(4-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-t-butyl-4[{di-t-butyl(2-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-methyl-4[(trimethylsilyl)methylthio]phenol

2,6-di-methyl-4[(dimethylphenylsilyl)methylthio]phenol

2,6-di-methyl-4[{dimethyl-(4-methoxyphenylsilyl)}methylthio]phenol

2,6-di-methyl-4[{dimethyl-(2-methoxyphenylsilyl)}methylthio]phenol

2,6-di-methyl-4[(dibutylphenylsilyl)methylthio]phenol

2,6-di-methyl-4[{dibutyl-(4-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-methyl-4[{dibutyl-(2-ethoxyphenyl)silyl}methylthio]phenol

2,6-di-methyl-4[(tri-t-butylsilyl)methylthio]phenol
2,6-di-methyl-4[(di-t-butylphenylsilyl)methylthio]phenol
2,6-di-methyl-4[{di-t-butyl-(4-methoxyphenyl)silyl}methylthio]phenol
2,6-di-methyl-4[{di-t-butyl-(2-methoxyphenyl)silyl}methylthio]phenol
2,6-di-ethyl-4[(trimethylsilyl)methylthio]phenol
2,6-di-ethyl-4[(dimethylphenylsilyl)methylthio]phenol
2,6-di-ethyl-4[(tri-t-butylsilyl)methylthio]phenol
2,6-di-ethyl-4[(di-t-butylphenylsilyl)methylthio]phenol
2,6-di-ethyl-4[{di-t-butyl-(4-methoxyphenyl)silyl}methylthio]phenol
2,6-di-ethyl-4[{di-t-butyl-(2-methoxyphenyl)silyl}methylthio]phenol
2,6-di-propyl-4[(trimethylsilyl)methylthio]phenol
2,6-di-propyl-4[(dimethylphenylsilyl)methylthio]phenol
2,6-di-propyl-4[(trimethylsilyl)methylthio]phenol
2,6-di-propyl-4[(dimethylphenylsilyl)methylthio]phenol
2,6-di-propyl-4[{dimethyl-(4-ethoxyphenyl)silyl}methylthio]phenol
2,6-di-propyl-4[{dimethyl-(2-ethoxyphenyl)silyl}methylthio]phenol
2,6-di-butyl-4[(trimethylsilyl)methylthio]phenol
2,6-di-butyl-4[(dimethylphenylsilyl)methylthio]phenol
2,6-di-methyl-4[(trimethylsilyl)methyloxy]phenol
2,6-di-methyl-4[(dimethylphenylsilyl)methyloxy]phenol
2,6-di-methyl-4[{dimethyl-(4-ethoxyphenyl)silyl}methyloxy]phenol
2,6-di-methyl-4[{dimethyl-(2-ethoxyphenyl)silyl}methyloxy]phenol
2,6-di-butyl-4[(triethylsilyl)methyloxy]phenol
2,6-di-butyl-4[(diethylphenylsilyl)methyloxy]phenol
2,6-di-butyl-4[{diethyl(4-methoxyphenyl)silyl}methyloxy]phenol
2,6-di-butyl-4[{diethyl(2-methoxyphenyl)silyl}methyloxy]phenol
2,6-di-t-butyl-4[(trimethylsilyl)methyloxy]phenol
2,6-di-t-butyl-4[(dimethylphenylsilyl)methyloxy]phenol
2,6-di-t-butyl-4[{dimethyl(4-methoxyphenyl)silyl}methyloxy]phenol
2,6-di-t-butyl-4[{dimethyl(2-methoxyphenyl)silyl}methyloxy]phenol
2,6-di-t-butyl-4[{dimethyl-(4-ethoxyphenyl)silyl)methyloxy]phenol
2,6-di-t-butyl-4[{dimethyl-(2-ethoxyphenyl)silyl)methyloxy]phenol

2,6-di-methyl-4[(trimethylsilyl)methyloxy]phenol

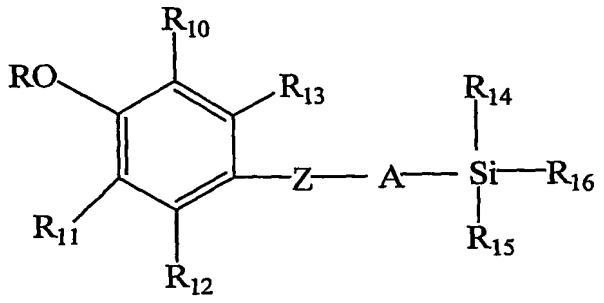
2,6-di-methyl-4[(dimethylphenylsilyl)methyloxy]phenol

2,6-di-butyl-4[(triethylsilyl)methyloxy]phenol

2,6-di-butyl-4[(diethylphenylsilyl)methyloxy]phenol

The above compounds are listed only to provide examples that may be used in the methods of the invention. Based upon the instant disclosure, the skilled artisan would recognize other compounds intended to be included within the scope of the presently claimed invention that would be useful in the methods recited herein.

In alternative methods of the invention, it may be advantageous to employ compounds of Formula (I) or Formula (II) that are not also within the definition of compounds of Formula (IV), which is shown below.



(IV)

wherein:

R_{10} and R_{15} are each independently $C_1 - C_6$ alkyl;

R_{11}, R_{12} and R_{13} are each independently hydrogen or $C_1 - C_6$ alkyl;

R is hydrogen or $-C(O)-(CH_2)_m-Q$, wherein Q is hydrogen or –COOH and m is an integer 1, 2, 3 or 4;

Z is a thio, oxy or methylene group;

A is a $C_1 - C_4$ alkylene group;

R_{14} and R_{16} are each independently a $C_1 - C_6$ alkyl or $-(CH_2)_n-(Ar)$, wherein n is an integer 0, 1, 2 or 3; and Ar is phenyl or naphthyl unsubstituted or substituted with one to three substituents selected from the group consisting of hydroxy, methoxy, ethoxy, halogen, trifluoromethyl, $C_1 - C_6$ alkyl, or $-NR_{17}R_{18}$, wherein R_{17} and R_{18} are each independently hydrogen or $C_1 - C_6$ alkyl; with the proviso that when R_{11} and at least one of R_{14} or R_{16} is $C_1 - C_6$ alkyl, and Ar is not substituted with

trifluoromethyl or $-NR_{17}R_{18}$, then R is $-C(O)-(CH_2)_m-Q$; or a pharmaceutically acceptable salt thereof.

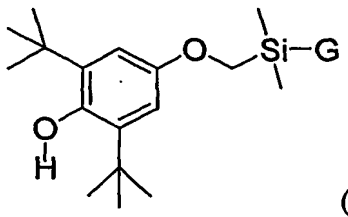
In another embodiment, it may be advantageous to employ compounds of Formula (I) or Formula (II) wherein at least one of R_8 or R_9 is independently selected from the group consisting of: trifluoromethyl, Br, amino, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, $-O(C_1-C_6$ alkyl), $-OCO-$(H or C_1-C_7 alkyl), $-OCO-(C_3-C_7$ alkenyl), $-OCO-$(aryl), $-OCO-$(heteroaryl), $-(C_0-C_8$ alkyl)-COOH, $-(C_2-C_8$ alkenyl)-COOH, $-OCO-(C_0-C_6$ alkyl)-COOH, $-OCO-(C_2-C_6$ alkenyl)-COOH, $-CO-(C_0-C_6$ alkyl)-COOH, and $-CO-(C_2-C_6$ alkenyl)-COOH; or any combination thereof. In other alternative embodiments useful in the methods of the invention, it may be advantageous to employ compounds of Formula (II) with the limiting proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both independently selected from hydroxy, ester, or ether; or alternatively, with the limiting proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both hydroxy.

It may additionally be advantageous to employ compounds of Formula (II) that are not a compound of Formula (IV) and which are subject to the proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both independently selected from hydroxy, ester, or ether; or alternatively, with the limiting proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both hydroxy.

In another embodiment, it may be advantageous to employ compounds of Formula (II) subject to the limiting proviso that at least one of R_8 or R_9 is independently selected from the group consisting of: trifluoromethyl, Br, amino, alkyl, alkenyl, aryl, heteroaryl, alkanoyl, aryloyl, heteroaryloyl, $-O(C_1-C_6$ alkyl), $-OCO-$(H or C_1-C_7 alkyl), $-OCO-(C_3-C_7$ alkenyl), $-OCO-$(aryl), $-OCO-$(heteroaryl), $-(C_0-C_8$ alkyl)-COOH, $-(C_2-C_8$ alkenyl)-COOH, $-OCO-(C_0-C_6$ alkyl)-COOH, $-OCO-(C_2-C_6$ alkenyl)-COOH, $-CO-(C_0-C_6$ alkyl)-COOH, and $-CO-(C_2-C_6$ alkenyl)-COOH; or any combination thereof; and either the limiting proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both independently selected from hydroxy, ester, or ether, or alternatively, the limiting proviso that when X_1 and X_2 are both thio, R_8 and R_9 are not both hydroxy.

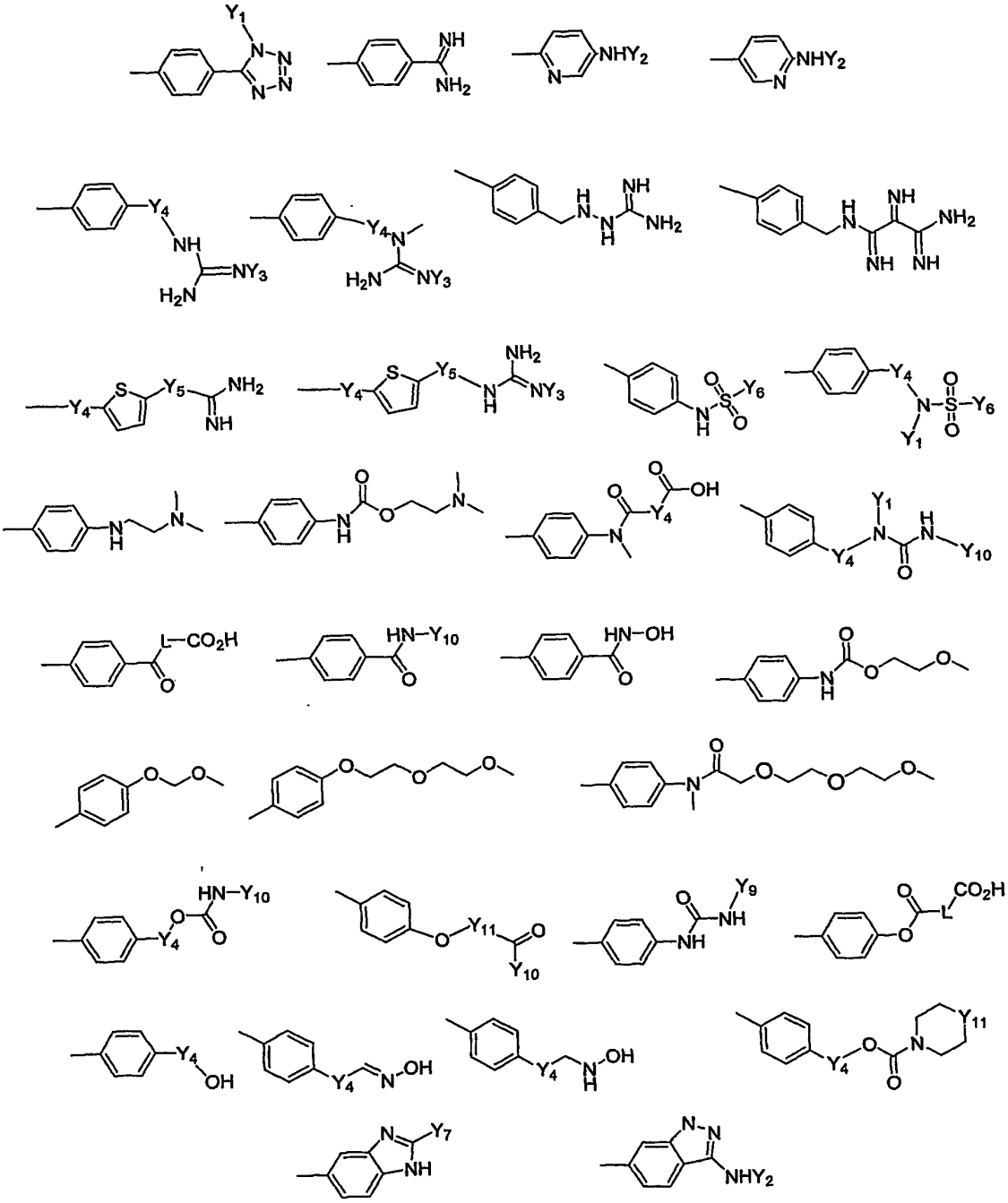
In a further embodiment, compounds of Formula (V), which is shown below, are provided. Compounds of Formula (V) are useful in the preparation of novel

compositions that may be employed in methods for the prophylaxis or therapeutic treatment of vascular access dysfunction,



(V)

wherein G is selected from the group consisting of:



wherein:

Y_1 is –H, C_1-C_4 alkyl, or C_3-C_6 alkenyl;

Y_2 is –H, C_1-C_4 alkyl, or C_3-C_6 alkenyl, aryl, heteroaryl, aryloyl, alkanoyl, or heteroaryloyl;

Y_3 is –H, –CN, C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl or heteroaryl;

Y_4 is $(CH_2)_n$, where n is 0-4, or C_3-C_6 alkenyl;

Y_5 is NH, $(CH_2)_n$, where n is 0-4, or C_2-C_6 alkenyl;

Y_6 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_7 is H, C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or NH-Y_8;

Y_8 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_9 is C_1-C_4 alkyl, C_3-C_6 alkenyl, aryl, or heteroaryl;

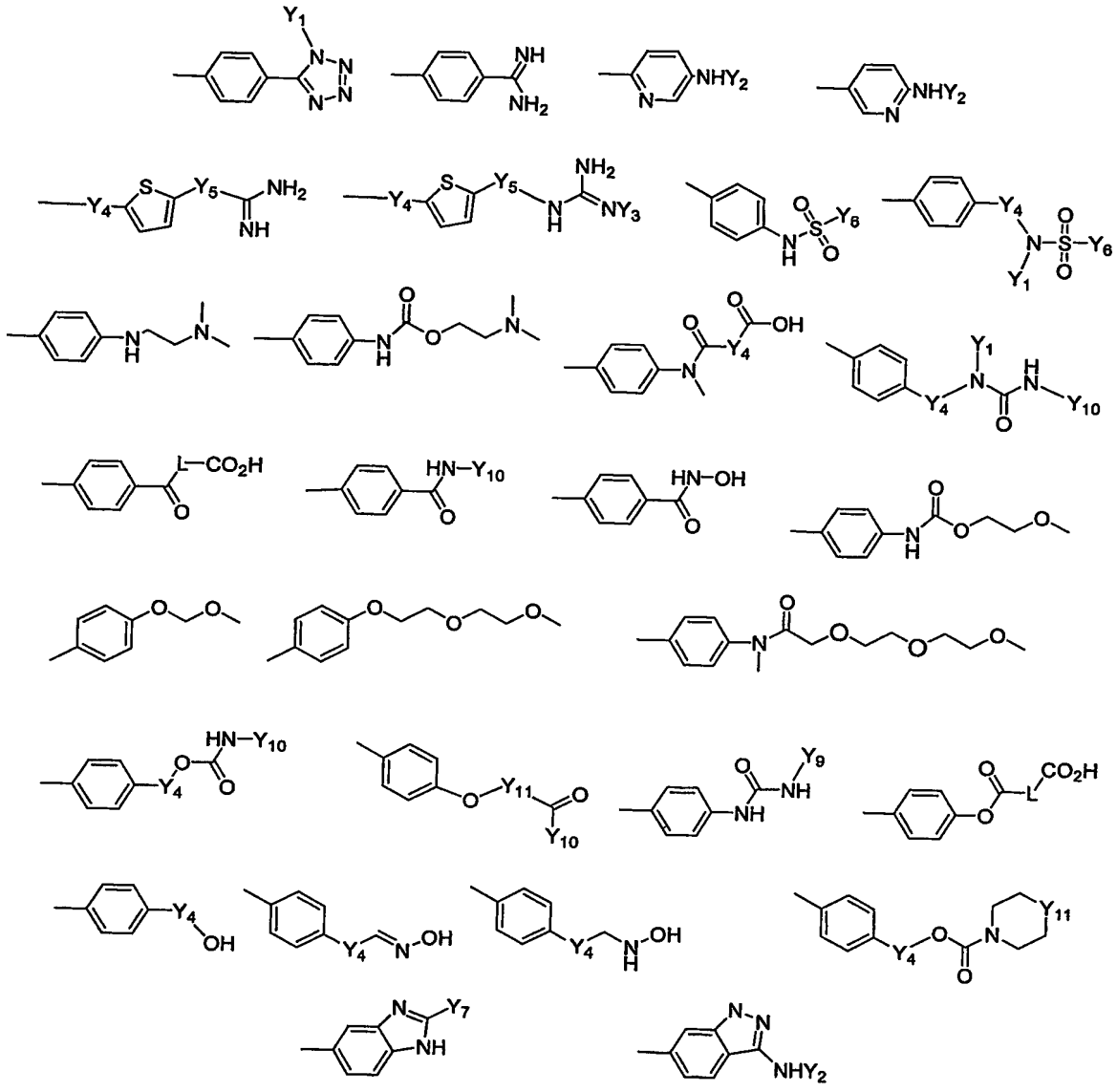
Y_{10} is H, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

Y_{11} is C_1-C_4 alkyl, C_3-C_6 alkenyl, -O-, or -N-(Y_1);

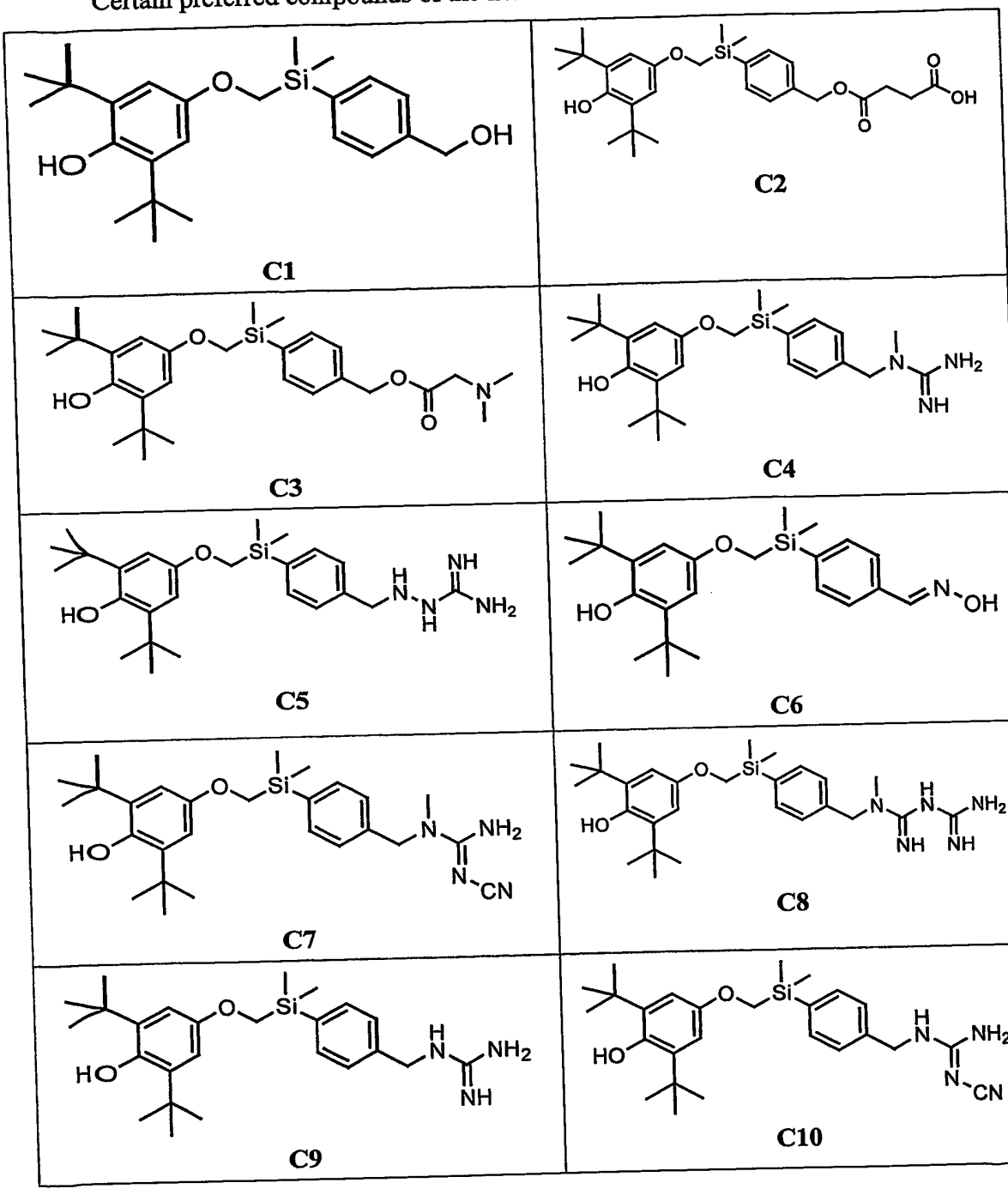
L is C_1-C_6 alkyl or C_2-C_6 alkenyl; and

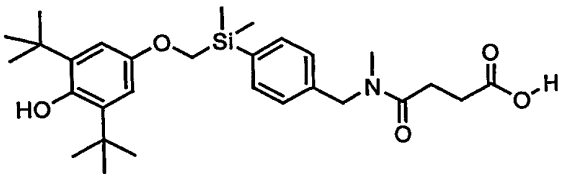
wherein G may be additionally substituted with one or more substituents independently selected from the group consisting of –F, –Cl, –Br, –I, $–NH_2$, alkyl-substituted amino, –OH, –CN, –SH, $–CH_3$, $–CH_2CH_3$, $–CF_3$, $–OCH_3$, $–OCH_2CH_3$, –COOH, $–COOCH_3$, and $–COOCH_2CH_3$.

In one embodiment of Formula (V), G does not include any guanidine groups. Alternatively, in a preferred embodiment of Formula (V), G is selected from:



Certain preferred compounds of the invention include:





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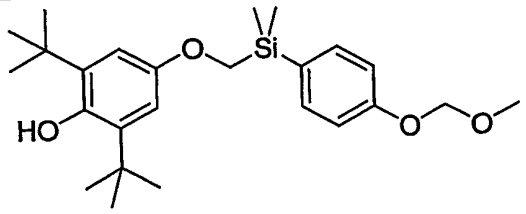
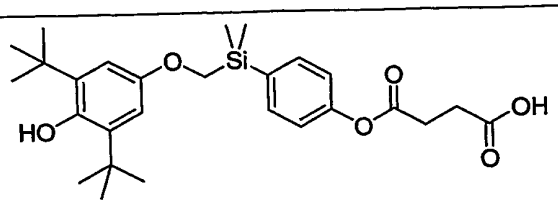
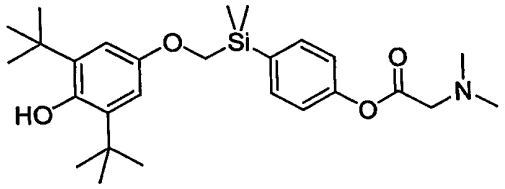


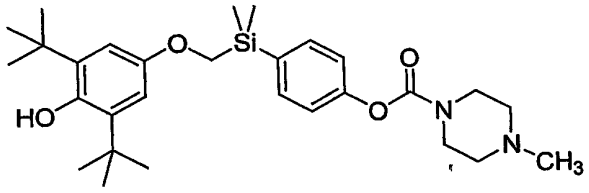
C12



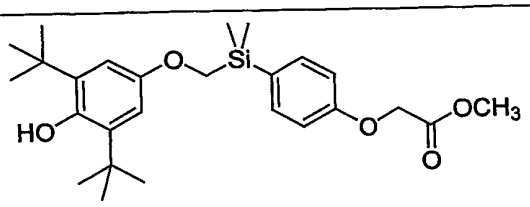
C13



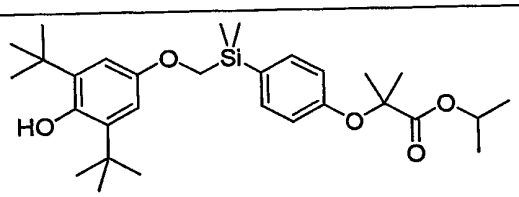
C14



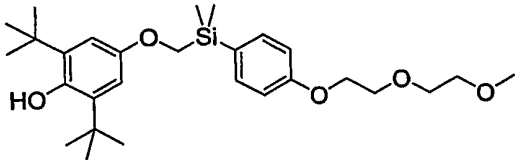
C15



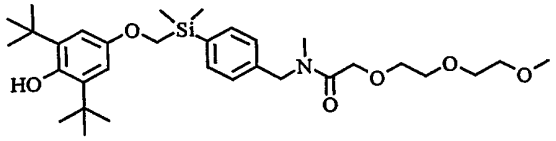
C16



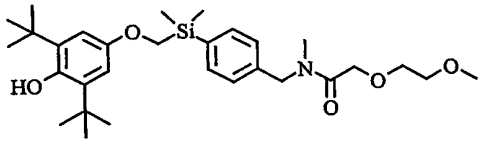
C17



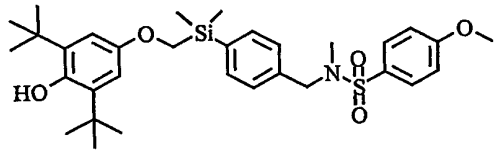
C18



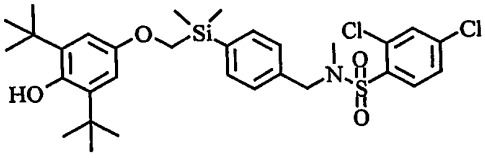
C19



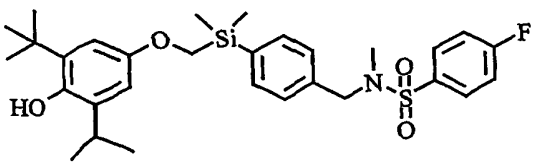
C20



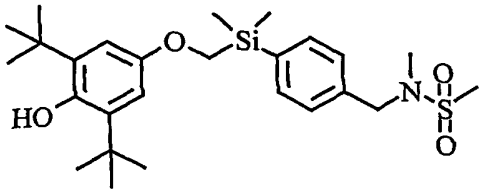
C21



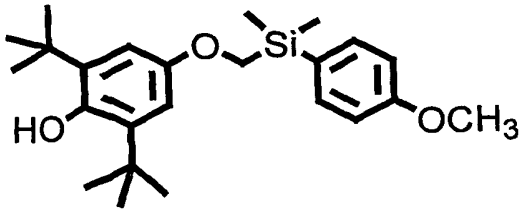
C22



C23

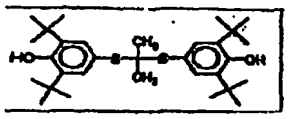
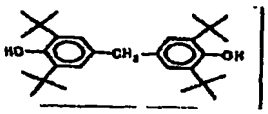
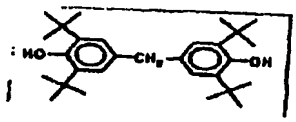
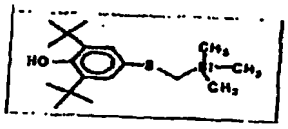
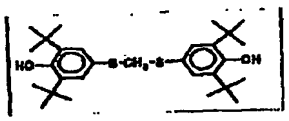
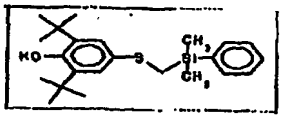
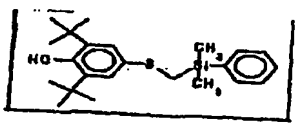
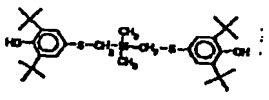


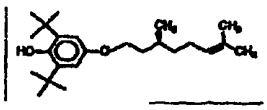
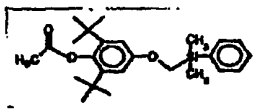
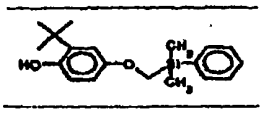
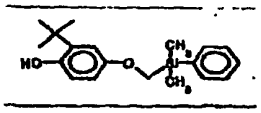
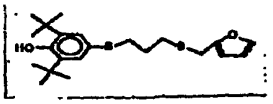
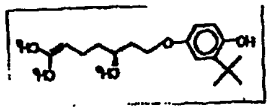
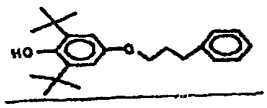
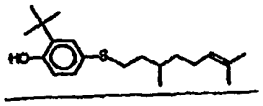
C24

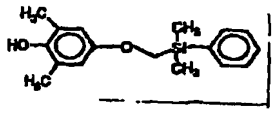
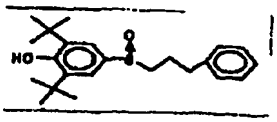
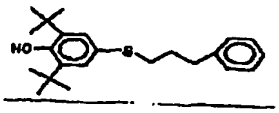
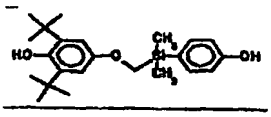
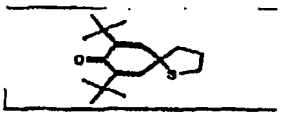
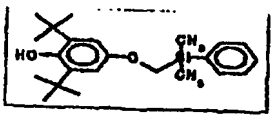
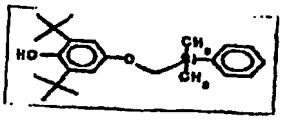
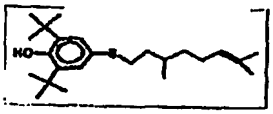


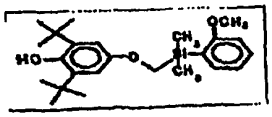
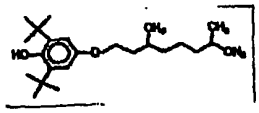
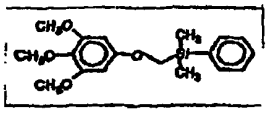
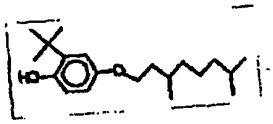
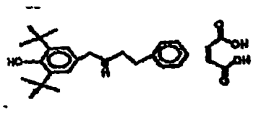
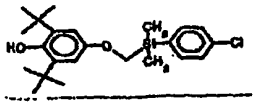
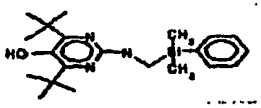
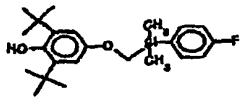
C25

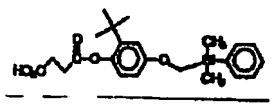
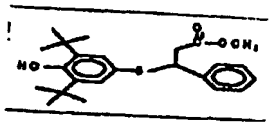
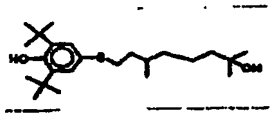
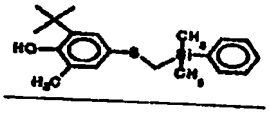
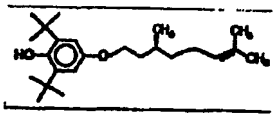
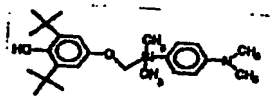
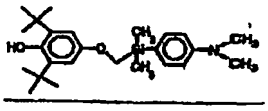
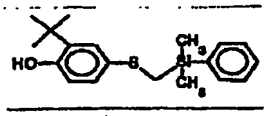
Other preferred compounds of the invention include:

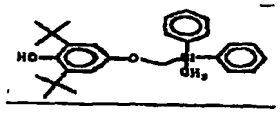
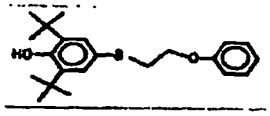
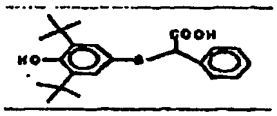
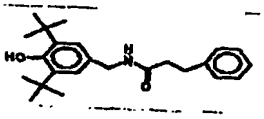
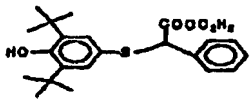
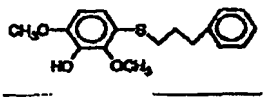
 C26	 C27
 C28	 C29
 C30	 C31
 C32	 C33

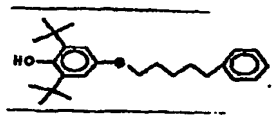
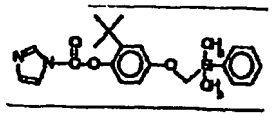
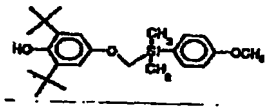
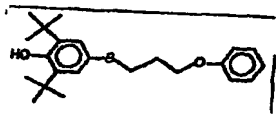
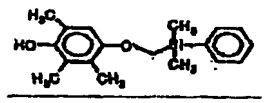
 C34	 C35
 C36	 C37
 C38	 C39
 C40	 C41

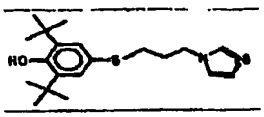
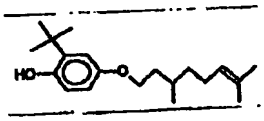
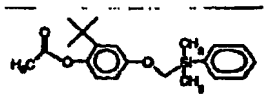
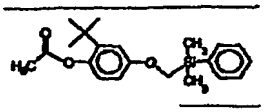
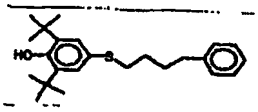
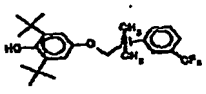
 C42	 C43
 C44	 C45
 C46	 C47
 C48	 C49

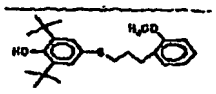
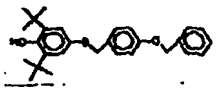
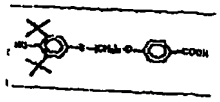
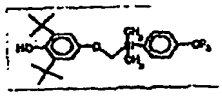
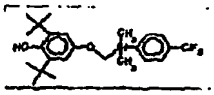
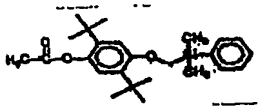
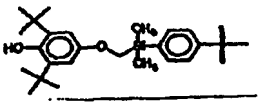
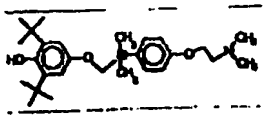
 C50	 C51
 C52	 C53
 C54	 C55
 C56	 C57

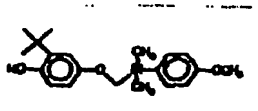
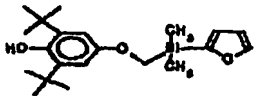
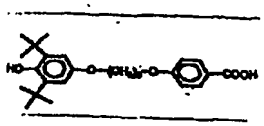
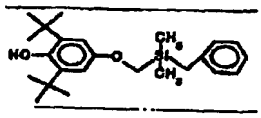
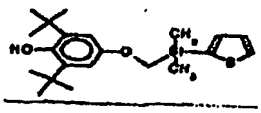
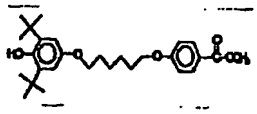
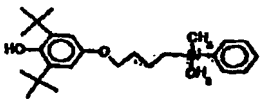
 C58	 C59
 C60	 C61
 C62	 C63
 C64	 C65

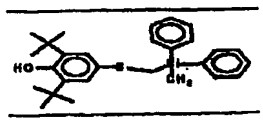
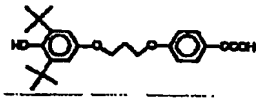
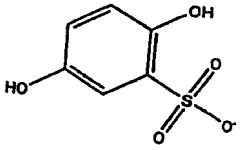
 C66	 C67
 C68	 C69
 C70	 C71

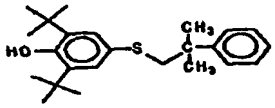
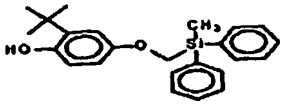
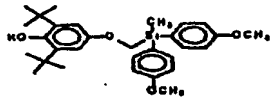
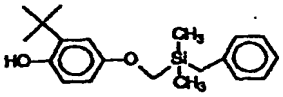
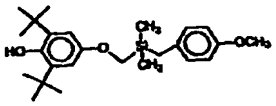
 C72	 C73
 C74	 C75
 C76	 C77

 C78	 C79
 C80	 C81
 C82	 C83

 C84	 C85
 C86	 C87
 C88	 C89
 C90	 C91

 C92	 C93
 C94	 C95
 C96	 C97
 C98	 C99

 C100	 C101
 C102	

 C103	 C104
 C105	 C106
 C107	

For the purposes of this invention, where one or more functionalities encompassing R_1-R_{14}, Y_1-Y_{10}, L, Z, A, and Ar, are incorporated into a molecule of Formulas (I) - (V), each the functionality appearing at any location within the structures of Formulas (I) - (V) may be independently selected, and as appropriate, independently substituted.

Where a more generic substituent is set forth for any position in the molecules of the present invention, it is understood that the generic substituent may be replaced with more specific substituents, and the resulting molecules are within the scope of the molecules of the present invention. Thus, for example if a substituent is recited as an alkyl group, molecules, and groups of molecules, having the substituent limited to C_1-C_6 alkyl are understood to be part of the present invention. Similarly, if more than one substituent is recited generically, then each may be replaced by more specifically recited substituents, and the resulting molecules are within the scope of the molecules of the present invention. Thus, for example, if the molecule recites a first substituent as alkenyl and second substituent as alkylaryl, it is understood that the first substituent may for example be limited to -($C_5 - C_{10}$ alkenyl) and the second may be limited to -(C_1-C_6 alkyl)-naphthalene.

As used herein, the term "alkyl" generally refers to saturated hydrocarbyl radicals of straight, branched or cyclic configuration including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, cyclohexyl, n-heptyl, octyl, n-octyl, and the like. Di-substituted alkyl generally refers to a hydrocarbyl radical substituted on its core with at least two substituents, R_2 and R_3. In some embodiments, alkyl substituents may be include $C_1 - C_{20}$ alkyl, $C_1 - C_{10}$ alkyl, $C_1 - C_8$ alkyl, C_1 - C_6 alkyl, or $C_5 - C_{10}$ alkyl.

As used herein, the terms halomethyl, dihalomethyl, or trihalomethyl refer to methyl radicals bearing one, two or three halogen substitutions, respectively.

The term "C_1 - C_4 alkylene" refers to a saturated hydrocarbyldiyl radical of straight or branched configuration made up of from one to four carbon atoms. Included within the scope of this term are methylene, 1,2-ethane-diyl, 1,1-ethane-diyl, 1,3-propane-diyl, 1,2-propanediyl, 1,3-butane-diyl, 1,4-butane-diyl and the like.

As used herein, the term alkenyl generally refers to hydrocarbyl radicals of straight, branched or cyclic configuration having at least one carbon-carbon double

bond in either the *cis* or *trans* configuration, or as a mixture of *cis* and *trans* isomers (*i.e.*, the radical of an alkene). Included in the scope of alkenyl are substituents having from three to about eight carbon atoms ($C_3 - C_8$ alkenyl), from four to six carbon atoms ($C_4 - C_6$ alkenyl), or from five to about ten carbons ($C_5 - C_{10}$ alkenyl). Examples of alkenyl substituents include -$CHCH_2$ group (*i.e.*, ethylene), a propen-1-yl group, a propen-2-yl group, and a *trans* -$CH_2CHCHCH_3$ group (*i.e.*, *trans*-2-butene).

As used herein, aryl refers to a carbocyclic aromatic ring structure. Included in the scope of aryl groups are aromatic rings having from six to twenty carbon atoms. In some embodiments, they may have from ten to twenty carbon atoms, and in others from fourteen to 24 carbon atoms. Examples of aryl groups that may be incorporated as substituents include phenyl, phenanthryl (*i.e.*, phenanthrene), and napthyl (*i.e.*, napthalene) ring structures.

As used herein, heteroaryl refers to cyclic aromatic ring structures in which one or more atoms in the ring, the heteroatom(s), is an element other than carbon. Heteroatoms are typically O, S or N atoms. Included within the scope of heteroaryl, and independently selectable are O, N, S and P heteroaryl ring structures. In some embodiments, the heteroaryl groups may be selected from heteroaryl groups that contain two or more heteroatoms, three or more heteroatoms, or four or more heteroatoms. Heteroaryl ring structures may be selected from those that contain five or more atoms, six or more atoms, or eight or more atoms. Examples of heteroaromatic ring structures that may be incorporated as substituent groups include, but are not limited to: acridine, benzimidazole, benzoxazole, benzofuran, 1,3-diazine, 1,2-diazine, 1,2-diazole, 1,4-diazanaphthalene, furan, furazan, imidazole, indole, isoxazole, isoquinoline, isothiazole, oxazole, purine, pyridazine, pyrazole, pyridine, pyrazine, pyrimidine, pyrrole, quinoline, quinoxaline, thiazole, thiophene, 1,3,5-triazine, 1,2,4-triazine, 1,2,3-triazine, tetrazole and quinazoline.

As used herein, the structure –O(alkyl) represents an alkylether, where alkyl is defined as above. Included in the scope of alkylether substituents are –O(C_1-C_6 alkyl), –O(C_2-C_8 alkyl), and –O(C_4-C_{10} alkyl). Examples of alkyl ethers include methoxy (*i.e.*, -OCH_3,), ethoxy (*i.e.*, -OCH_2CH_3,), and tert-butyl ethers (*i.e.*, -$OC(CH_3)_3$).

As used herein, the structure –OCO-(H or alkyl) represents an alkyl ester group, where alkyl is defined as above. When the structure is –OCO-(H), the substituent group will be a formate ester. Included in the scope of alkylesters are -OCO-(H or C_1-C_7 alkyl), –OCO-(H or C_3-C_9 alkyl), -OCO-(C_1-C_7 alkyl), and –OCO-(C_3-C_9 alkyl). Examples of alkyl esters include –$OCOCH_3$ (*i.e.*, acetoxy), –$OCOCH_2CH_3$ (*i.e.*, propionate ester).

As used herein, the structure –OCO-(alkenyl) represents an alkenyl ester group, where alkenyl is defined as above. Included in the scope of alkenyl esters are -OCO-(C_2-C_8 alkenyl), -OCO-(C_3-C_8 alkenyl), and –OCO-(C_5-C_9 alkenyl). Alkenyl esters maybe in the *cis* or *trans* isomers or mixtures of both *cis* and *trans* isomers. Examples of alkenyl esters include –$OCOCHCHCH_3$ (*i.e.*, 2-butenoate), –$OCOCHCHCH_2CH_3$ (*i.e.*, 2-pentenoate).

As used herein, the structure –(alkyl)-COOH generally refers to saturated hydrocarboxyl radicals (alkyl carboxylic acid) of straight, branched, or cyclic configuration, with –(C_0-C_8 alkyl)-COOH radicals having between one and nine carbon atoms in total. Included in the scope of alkylesters are –(alkyl)-COOH radicals having between one and nine carbon atoms –(C_0-C_8 alkyl)-COOH, or between five and twelve carbon atoms –(C_4-C_{11} alkyl)-COOH. Such hydrocarboxyl radicals include methanoic acid, ethanoic acid, propanoic acid, butanoic acid, 2-methyl propanoic acid, pentanoic acid, 3-methyl butanoic acid, 2,2-dimethyl propanoic acid, and the like. Likewise, the structure –(alkenyl)-COOH generally refers to saturated hydrocarboxyl radicals where alkenyl is defined above. In addition to those alkyl esters recited as included in the scope of –(alkyl)-COOH above, in some embodiments, the group may be selected from structures with three to nine carbon atoms –(C_2-C_8 alkenyl)-COOH, and in other embodiments, the group may be selected from structures having five to ten carbon atoms –(C_4-C_9 alkenyl)-COOH.

As used herein, the structure –OCO-(alkyl)-COOH (alkyl dicarboxylic acid) generally refers to saturated hydro-dicarboxyl radicals of straight, branched or cyclic configuration, and –OCO-(C_0-C_6 alkyl)-COOH generally refers to dicarboxylic acids having between two and eight carbon atoms. Alkyl dicarboxylic acids may be selected from structures within the scope of –OCO-(alkyl)-COOH, including the structures -OCO-(C_0-C_6 alkyl)-COOH, –OCO-(C_0-C_8 alkyl)-COOH, and –OCO-(C_5-

C_{10} alkyl)-COOH. Alkyl dicarboxylic acids include ethandioic acid, propandioic acid, butandioic acid (*e.g.*, succinic acid, 2-methyl-propandioic acid, pentandioic acid (*i.e.*, glutaric acid), 3-methyl-butandioic acid, hexandioic acid, and the like).

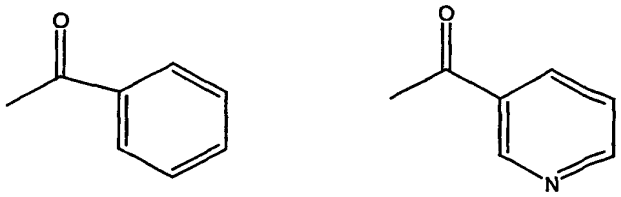
As used herein, the structure –OCO-(alkenyl)-COOH generally refers to hydro-dicarboxyl radicals having at least one carbon-carbon double bond of straight, branched or cyclic configuration. Carbon-carbon double bonds may be in the *cis* or *trans* configuration or may be present as a mixture of *cis* and *trans* isomers. Alkenyl oxydicarbonyls (alkenyl dicarboxylic acids) may selected from structures included within the scope of –OCO-(alkenyl)-COOH including the structure –OCO-(C_2-C_6 alkenyl)-COOH, where the group has up to eight carbon atoms and the structure –OCO-(C_5-C_{10} alkenyl)-COOH where it has up to twelve carbon atoms. Alkenyl oxydicarbonyls include *trans*-2-butenedioic acid (*e.g.*, fumaric acid, *cis*-2-butenedioic acid (*i.e.*, maleic acid), 2-pentenedioic acid, 3-methyl-2-pentenedioic 2-pentendioic butandioic acid, hexandioic acid, and the like).

As used herein, –CO–(alkyl)–COOH and –CO–(alkenyl)-COOH represent saturated and unsaturated ketocarboxylic acid radicals of straight, branched or cyclic configuration where alkyl and alkenyl are as defined above. Ketocarboxylic acids may be independently selected from structures included within the scope of structures –CO–(alkyl)–COOH and –CO–(alkenyl)-COOH. Alkyl ketocarboxylic acids can be selected from –CO–(C_0-C_6 alkyl)–COOH and –CO–(C_3-C_9 alkyl)–COOH. Alkenyl ketocarboxylic acids can be selected from –CO–(C_2-C_6 alkenyl)-COOH and –CO–(C_4-C_{10} alkenyl)-COOH. Ketoalkyl carboxylic acids of the form –CO–(alkyl)–COOH include 6-keto-hexanoic acid, 5-keto-pentanoic, 5-keto-3-metyl-pentanoic, 3-keto-propanoic acid, and 2-keto-ethanoic acid. Ketoalkenyl carboxylic acids of the form –CO–(alkenyl)-COOH include 4-keto-2-butenoic acid, 5-keto-3-pentenoic acid, 6-keto-3-hexenoic acid, and 6-keto-3-methyl-2,4-hexadienoic acid.

As used herein, alkanoyl generally refers to a group with the structure –CO-(H or alkyl), where alkyl is defined above. When the group is of the form –COH the group will be an aldehyde. Alkanoyl groups included within the structure of –CO-(H or alkyl) include those with one to twenty carbons –CO-(C_1-C_{20} alkyl). In other embodiments, alkanoyl groups may be selected from those with three to twenty

carbon atoms, CO-(C_3-C_{20} alkyl), or from five to twenty carbon atoms, CO-(C_5-C_{20} alkyl), or from seven to twenty carbon atoms CO-(C_7-C_{20} alkyl).

As used herein, aryloyl refers to a structure of the form –CO-(aryl), where aryl is defined as above. Similarly, heteroaryloyl refers to a group of the formula –CO-(heteroaryl), where heteroaryl is defined as above. Aryloyl and heteroaroyl groups may be independently selected to contain the aryl and heteroaryl groups recited above. Examples of aryloyl and heteroaryloyl groups include the following structures:



As used herein, the structures –OCO-(aryl) and –OCO-(heteroaryl) generally refer to aromatic and heteroaromatic carboxylic acid functionalities (aryloxy and heteroaryloxy) addition that are present as ester substituents, where aryl and heteroaryl are as described above. The –OCO-(aryl) and –OCO-(heteroaryl) groups may be independently selected to contain the aryl and heteroaryl groups recited above. Aryl carboxylic acids include –OCO-phenyl, (*i.e.*, benzoate esters), and the like. Heteroaromatic carboxylic acid functionalities include 2-carboxy-pyridine, 2-carboxy-pyrrole, and 2-carboxy-furan.

For the purposes of this invention, halo substituents may be independently selected from the halogens such as fluorine, chlorine, bromine, iodine, and astatine.

Also included within the scope of the present invention are pharmaceutically acceptable salts, hydrates, solvates, clathrates, racemates, stereoisomers, or polymorphs of the compounds of the invention.

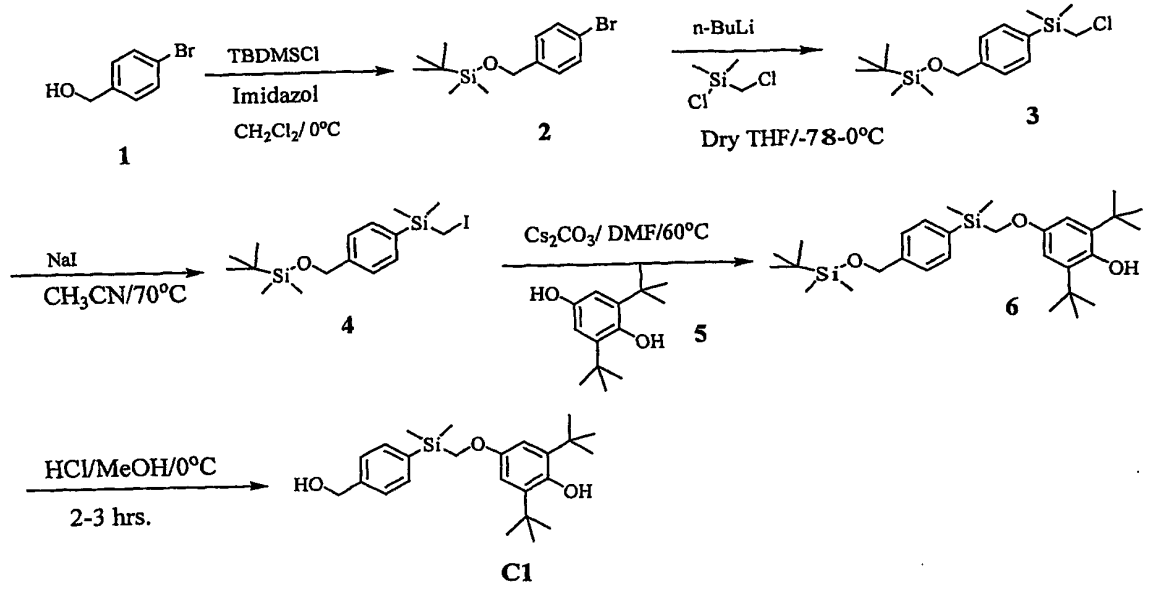
C. Preparation of Compounds of the Invention

Compounds of the invention may be produced in any manner known in the art. As mentioned above, the compounds of the invention are structurally related to probucol, 2,[3]-tert-butyl hydroxyanisole (BHA), 2,6-di-tert-butyl methylphenol (BHT), and other 2,6-di-alkyl phenols known in the art. As such, the compounds of the present invention may be synthesized in any manner similar to those known in the art for synthesis of 2,6-di-alkyl phenols (*e.g.*, U.S. Patent No. 5,155,250 and

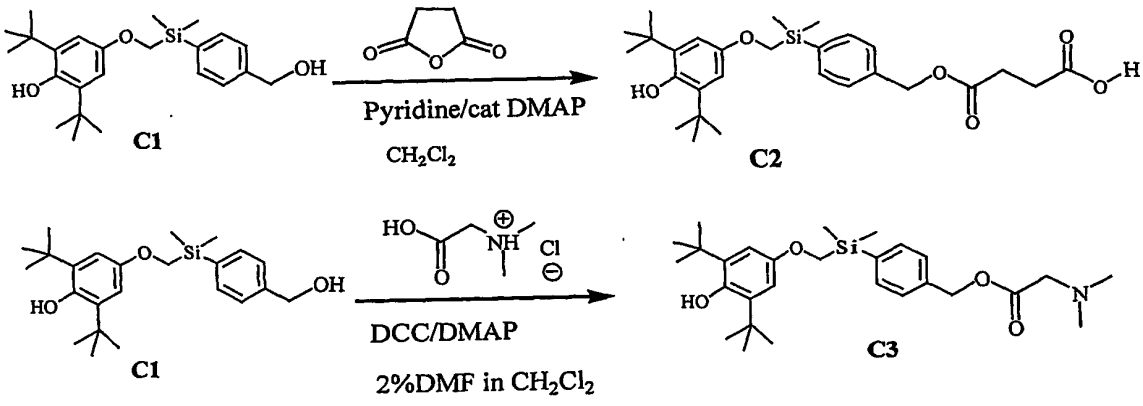
5,677,291, the contents of which are herein incorporated by reference in their entireties).

By way of example, certain preferred compounds of the invention may be prepared according to the following general schemes.

The benzylalcohol derivatives of the invention may be synthesized generally in accordance with **Schemes 1** and **2**, as follows:

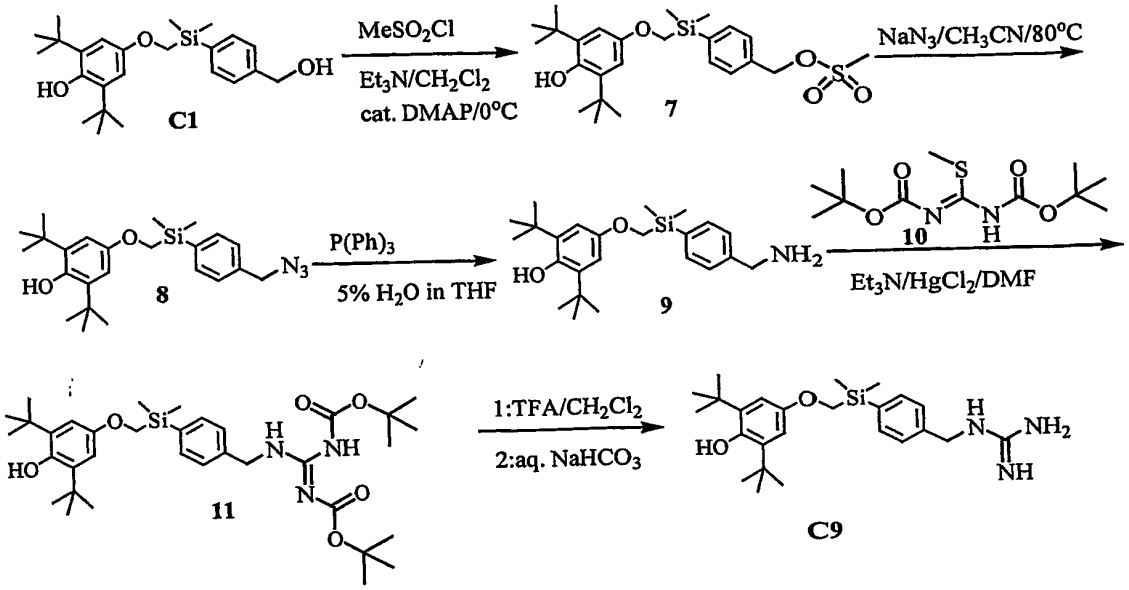


Scheme 1

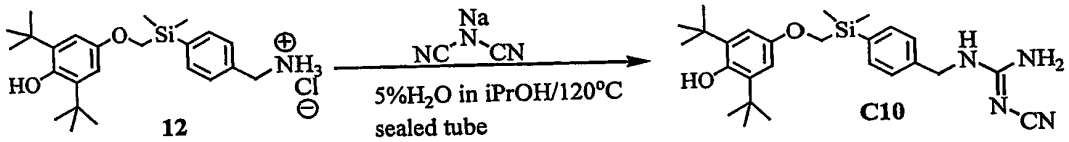


Scheme 2

The benzylamine derivatives of the invention may be synthesized generally in accordance with **Schemes 3, 4, 5,** and **6,** as follows:

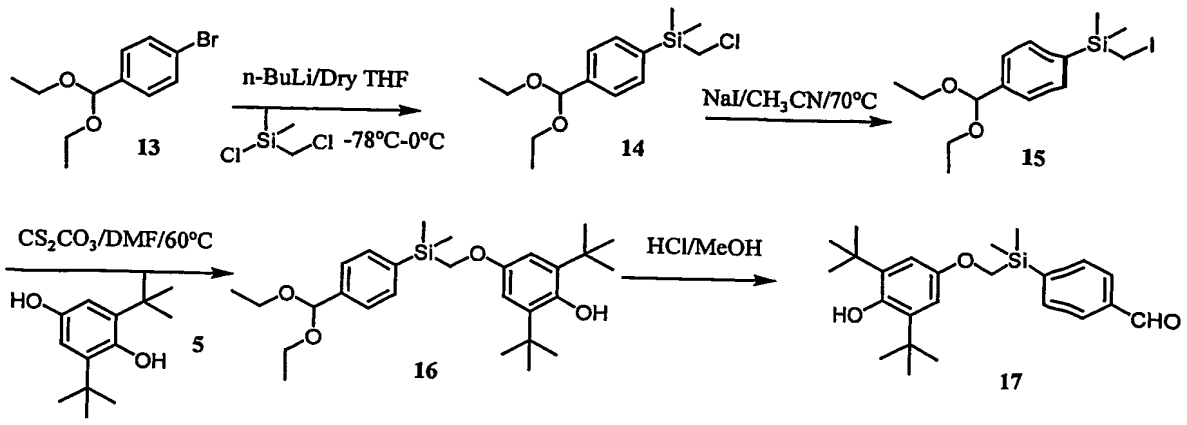


Scheme 3

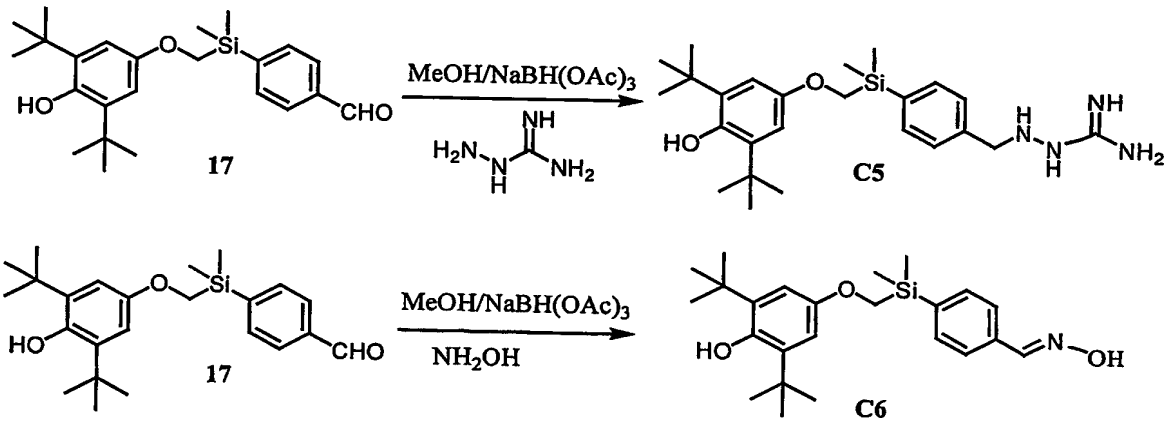


Scheme 4

Scheme 4

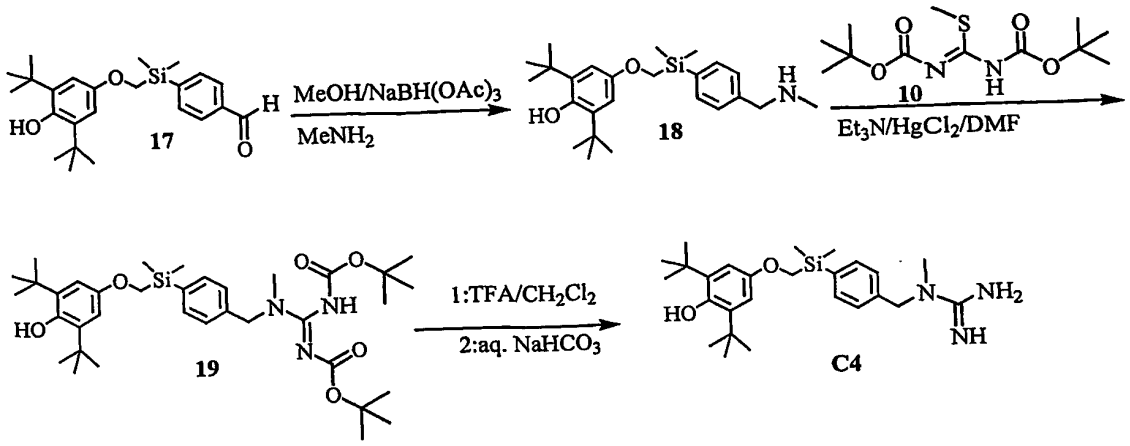


Scheme 5

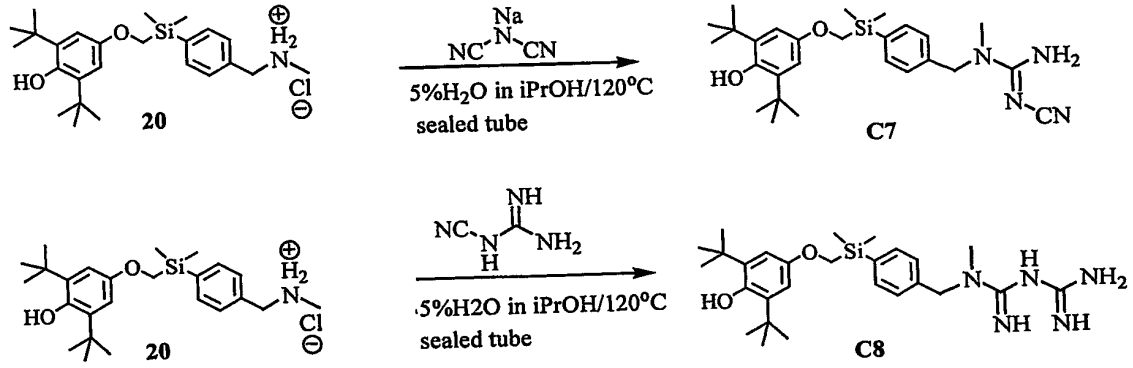


Scheme 6

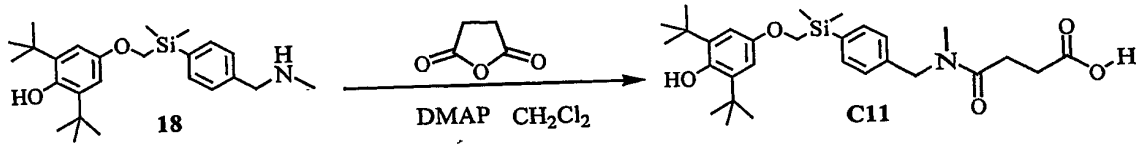
The N-methylbenzylamine derivatives of the invention may be synthesized generally in accordance with **Schemes 7, 8,** and **9**, as follows:



Scheme 7

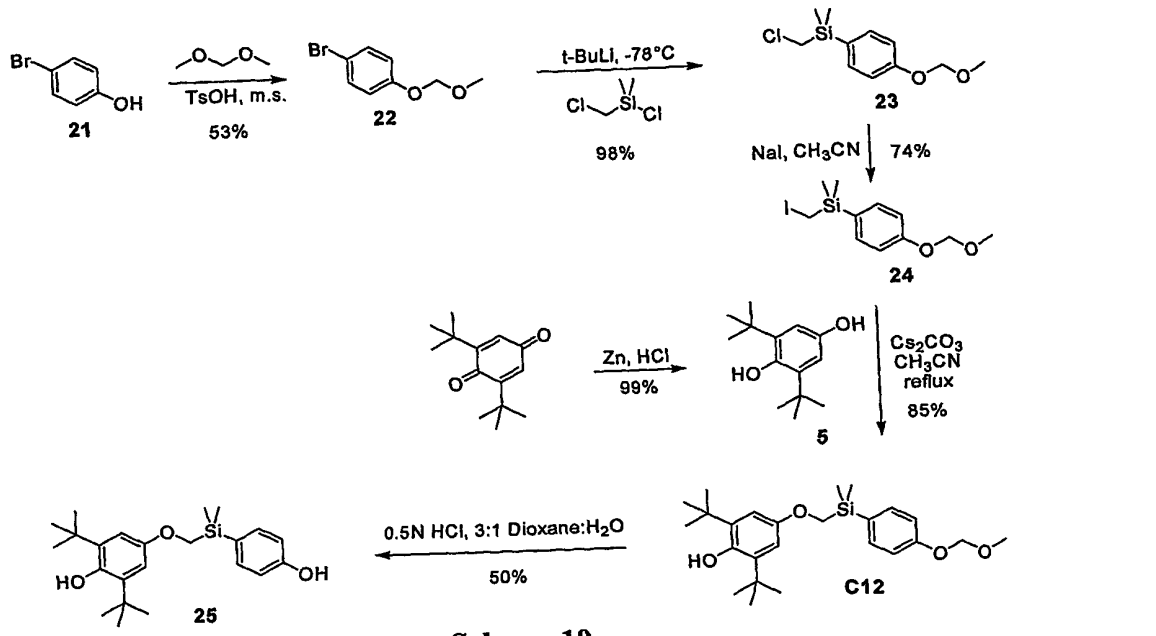


Scheme 8



Scheme 9

The phenolic derivatives of the invention may be synthesized generally in accordance with **Schemes 10, 11, 12,** and **13,** as follows: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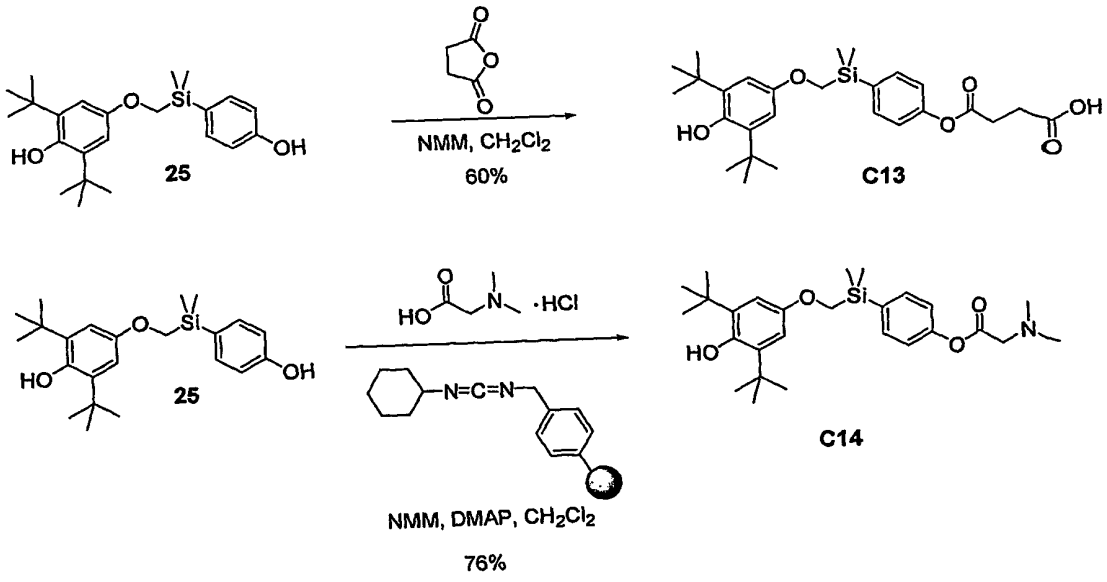
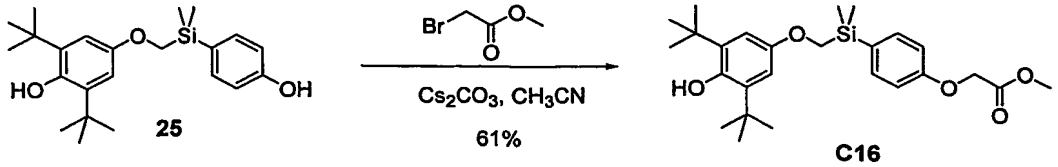
OH
21
TsOH, m.s.
53%
22
t-BuLi, -78°C
98%
23
NaI, CH3CN
74%
24
Zn, HCl
99%
Cs2CO3
CH3CN
reflux
85%
5
0.5N HCl, 3:1 Dioxane:H2O
50%
25
C12

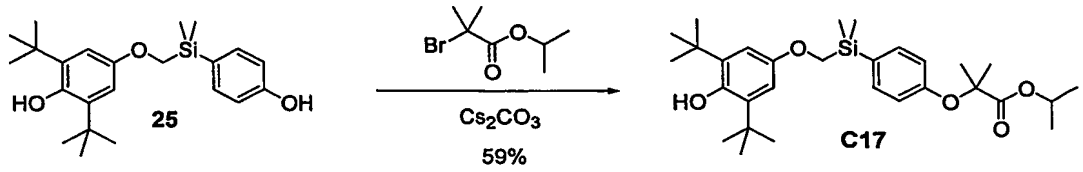
Scheme 10


25
NMM, CH2Cl2
60%
C13
·HCl
N=C=N
NMM, DMAP, CH2Cl2
76%
C14
1)
NO2
NMM. CH2Cl2
2)
, CH2Cl2
64%
C15

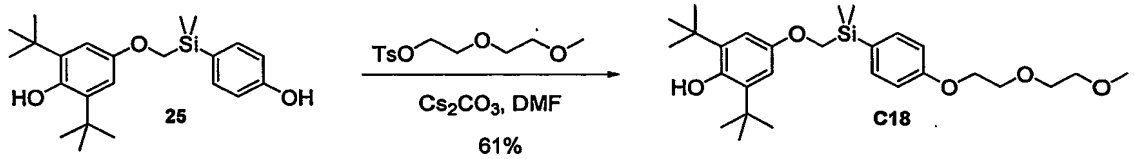
5

Scheme 11



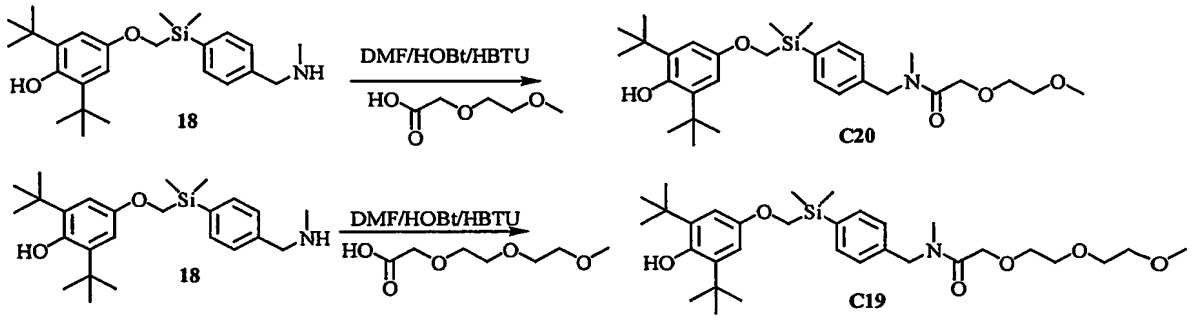


Scheme 12



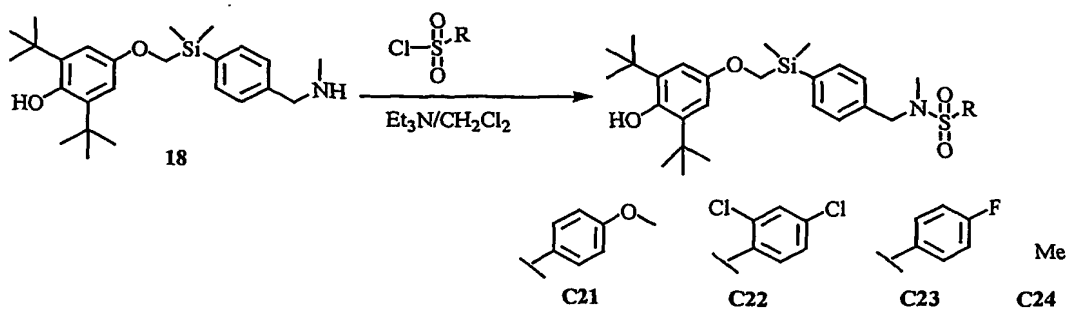
Scheme 13

The N-methylbenzylamide derivatives of the invention may be synthesized generally in accordance with **Scheme 14** as follows:



Scheme 14

The sulphonamide derivatives of the invention may be synthesized generally in accordance with **Scheme 15** as follows:



Scheme 15

D. Metabolites of the Compounds of the Invention

Also falling within the scope of the present invention are the *in vivo* metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radio-labeled (*e.g.* C^{14} or H^3) compound of the invention, administering it in a detectable dose (*e.g.*, greater than about 0.5 mg/kg) to a mammal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours), and isolating its conversion products from urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, *e.g.*, by MS or NMR analysis. In general, analysis of metabolites may be done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no biological activity of their own.

E. Pharmaceutical Compositions of the Invention

While it is possible for the compounds of the present invention to be

administered neat, it may be preferable to formulate the compounds as pharmaceutical compositions. As such, in yet another aspect of the invention, pharmaceutical compositions useful in the prophylaxis or therapeutic treatment of vascular access dysfunction are provided. The pharmaceutical compositions of the invention may be formulated with pharmaceutically acceptable excipients such as carriers, solvents, stabilizers, adjuvants, diluents, *etc.*, depending upon the particular mode of administration and dosage form. The pharmaceutical compositions should generally be formulated to achieve a physiologically compatible pH, and may range from a pH of about 3 to a pH of about 11, or about pH 3 to about pH 7, depending on the formulation and route of administration. In alternative embodiments it may be preferred that the pH is adjusted to a range from about pH 5.0 to about pH 8.0.

More particularly, the pharmaceutical compositions of the invention comprise a therapeutically or prophylactically effective amount of at least one compound of the present invention, together with one or more pharmaceutically acceptable excipients. Optionally, the pharmaceutical compositions of the invention may comprise a combination of compounds of the present invention, or may include a second active ingredient useful in the therapeutic or prophylactic treatment of vascular access dysfunction.

Formulations of the present invention, *e.g.*, for parenteral or oral administration, are most typically solids, liquid solutions, emulsions or suspensions, while inhaleable formulations for pulmonary administration are generally liquids or powders, with powder formulations being generally preferred. Pharmaceutical compositions of the invention may also be formulated as a lyophilized solid that is reconstituted with a physiologically compatible solvent prior to administration. Additional pharmaceutical compositions of the invention may be formulated as syrups, creams, ointments, tablets, and the like.

The term "pharmaceutically acceptable excipient" refers to an excipient for administration of a pharmaceutical agent, such as the compounds of the present invention. The term refers to any pharmaceutical excipient that may be administered without undue toxicity. Pharmaceutically acceptable excipients are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there exists a wide variety of

suitable formulations of pharmaceutical compositions of the present invention (*see, e.g.*, Remington's Pharmaceutical Sciences).

Suitable excipients may be carrier molecules that include large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive virus particles. Other exemplary excipients include antioxidants such as ascorbic acid; chelating agents such as EDTA; carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, and stearic acid; liquids such as oils, water, saline, glycerol and ethanol; wetting or emulsifying agents; pH buffering substances; and the like. Liposomes are also included within the definition of pharmaceutically acceptable excipients.

The pharmaceutical compositions of the invention may be formulated in any form suitable for the intended method of administration. When intended for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, non-aqueous solutions, dispersible powders or granules (including micronized particles or nanoparticles), emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation.

Pharmaceutically acceptable excipients particularly suitable for use in conjunction with tablets include, for example, inert diluents, such as celluloses, calcium or sodium carbonate, lactose, calcium or sodium phosphate; disintegrating agents, such as croscarmellose sodium, cross-linked povidone, maize starch, or alginic acid; binding agents, such as povidone, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example

celluloses, lactose, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with non-aqueous or oil medium, such as glycerin, propylene glycol, polyethylene glycol, peanut oil, liquid paraffin or olive oil.

In another embodiment, pharmaceutical compositions of the invention may be formulated as suspensions comprising a compound of the present invention in admixture with at least one pharmaceutically acceptable excipient suitable for the manufacture of a suspension. In yet another embodiment, pharmaceutical compositions of the invention may be formulated as dispersible powders and granules suitable for preparation of a suspension by the addition of suitable excipients.

Excipients suitable for use in connection with suspensions include suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, and gum acacia; dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycethanol), and a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate); and thickening agents, such as carbomer, beeswax, hard paraffin and cetyl alcohol. The suspensions may also contain one or more preservatives such as acetic acid, methyl and/or n-propyl p-hydroxy-benzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil; a mineral oil, such as liquid paraffin; or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth; naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids; hexitol anhydrides, such as sorbitan monooleate; and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with

sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

Additionally, the pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous emulsion or oleaginous suspension. This emulsion or suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,2-propane-diol. The sterile injectable preparation may also be prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

Generally, the compounds of the present invention useful in the methods of the present invention are substantially insoluble in water and are sparingly soluble in most pharmaceutically acceptable protic solvents and in vegetable oils. However, the compounds are generally soluble in medium chain fatty acids (*e.g.*, caprylic and capric acids) or triglycerides, and have high solubility in propylene glycol esters of medium chain fatty acids. Also contemplated in the invention are compounds which have been modified by substitutions or additions of chemical or biochemical moieties which make them more suitable for delivery (*e.g.*, increase solubility, bioactivity, palatability, decrease adverse reactions, *etc.*), for example by esterification, glycation, PEGylation, etc.

In one embodiment, the compounds of the present invention may be formulated for oral administration in a self-emulsifying drug delivery system (SEDDS). Lipid-based formulations such as SEDDS are particularly suitable for low solubility compounds, and can generally enhance the oral bioavailability of such compounds. As such, a pharmaceutical composition of the invention comprises a therapeutically or prophylactically effective amount of a compound of the present invention, together with at least one pharmaceutically acceptable excipient selected

from the group consisting of: medium chain fatty acids, propylene glycol esters thereof (*e.g.*, propylene glycol esters of edible fatty acids such as caprylic and capric fatty acids), and pharmaceutically acceptable surfactants such as polyoxyl 40 hydrogenated castor oil. [see *e.g.*, formulations described in SEDDS application, discussed *supra*].

In an alternative preferred embodiment, cyclodextrins may be added as aqueous solubility enhancers. Cyclodextrins include hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α-, β-, and γ-cyclodextrin. A particularly cyclodextrin solubility enhancer is hydroxypropyl-β-cyclodextrin (HPBC), which may be added to any of the above-described compositions to further improve the aqueous solubility characteristics of the compounds of the present invention. In one embodiment, the composition comprises 0.1% to 20% hydroxypropyl-β-cyclodextrin, 1% to 15% hydroxypropyl-β-cyclodextrin, or 2.5% to 10% hydroxypropyl-β-cyclodextrin. The amount of solubility enhancer employed will depend on the amount of the compound of the present invention in the composition.

F. Combination Therapy

It is also possible to combine any compound of the present invention with one or more other active ingredients useful in the prophylaxis or therapeutic treatment of MACEs, vascular access dysfunction, or male erectile dysfunction including compounds, in a unitary dosage form, or in separate dosage forms intended for simultaneous or sequential administration to a patient in need of treatment. When administered sequentially, the combination may be administered in two or more administrations. In an alternative embodiment, it is possible to administer a compound of the present invention and an additional active ingredient by different routes.

The skilled artisan will recognize that a variety of active ingredients may be administered in combination with the compounds of the present invention that may act to augment or synergistically enhance the response of a subject to a compound of the present invention. For instance, because the normal penile erection reaction results from a series of events giving rise to activation of the enzymes NO-synthase (NOS) and guanylyl cyclase, which leads to increased NO and cyclic guanosine monophosphate (cGMP), either substrates for these enzymes, or inhibitors of NO and

cGMP degradation may be employed to enhance the erectile response. Thus, the compounds of the present invention may be administered in combination with either sildenafil or like compounds (*e.g.*, vardenafil), which inhibit selectively the phosphodiesterase type 5 (PDE5), and thus prevents the decrease of cGMP, or with L-arginine, which is a substrate for NO-synthase, or with both sildenafil and L-arginine. Other active ingredients that may be administered with the compounds of the present invention include: the NOS cofactors NAD(P)H or tetrahydrobiopterin; the amino acids L-citrulline, L-orinithine, L-lysine, L-cysteine, or their salts or esters; flavoinoids; or plant extracts, including, but not limited to ginkgo biloba and bioflavonoids.

According to the methods of the invention, the combination of active ingredients may be: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by any other combination therapy regimen known in the art. When delivered in alternation therapy, the methods of the invention may comprise administering or delivering the active ingredients sequentially, *e.g.*, in separate solution, emulsion, suspension, tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.*, serially, whereas in simultaneous therapy, effective dosages of two or more active ingredients are administered together. Various sequences of intermittent combination therapy may also be used.

EXAMPLES

Pharmacologic studies may be performed focusing on mechanisms of action believed to be responsible for major adverse cardiac events in patients with an increased oxidative burden or elevated oxidative stress, such as hemodialysis, ESRD, and diabetic patients. Pharmacologic studies may also be performed focusing on mechanisms of action believed to be responsible for statin and fibrate refractive vascular occlusion, such as that observed in vascular access dysfunction. Further, pharmacologic studies may be performed focusing on mechanisms of action believed to be responsible for erectile dysfunction. Potential mechanisms include but are not limited to increases in serum antioxidant levels, inhibition of cytokine-induced

expression of VCAM-1, retention of normal vasodilatory responses, prevention of normal NO activity loss caused by tumor necrosis factor alpha (TNF-α) or quenching by ROS, induction of HMOX-1 expression, modulation of inflammation, and response to vascular injury or distress.

Pharmaceutical compositions comprising the compounds of the present invention may be formulated as described herein, and compared to similarly structured t-butyl phenol compounds such as probucol where appropriate.

Animal studies directly measuring effect of the compounds of the present invention on erectile dysfunction and in a rat diabetic model may also be employed. In addition, it is possible to evaluate the compounds of the instant invention employing human corpus cavernosum tissue.

Throughout these studies pharmaceutical compositions comprising the compounds of the present invention may be formulated as described herein, and compared to similarly structured t-butyl phenol compounds such as probucol where appropriate.

Example 1: Antioxidant Activity *In Vivo* Following Oral Administration

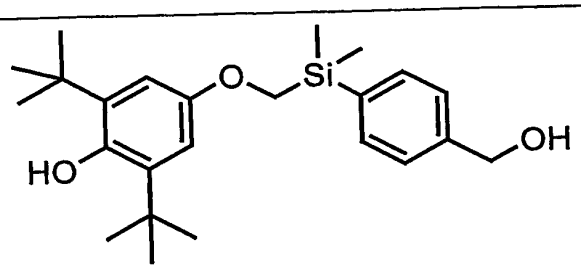
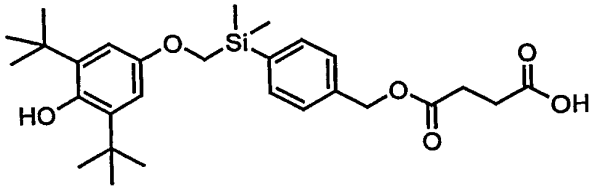
The compounds of the invention are also shown to increase serum antioxidant activity through *in vivo* studies in which various amounts of the compounds of the present invention are administered to a subject as an admixture in the diet using a Thiobarbituric Acid Reactive Substances (TBARS) assay. TBARS are a qualitative indication of the oxidation of lipids in a sample. In this assay, the oxidation of serum lipids is initiated with $CuSO_4$, resulting in the formation of aldehydes, such as malondialdehyde (MDA). Upon incubation with thiobarbituric acid, the absorbance of the aldehydes can be detected at 530-540 nm. TBARS values which are lower than control serum values indicate the relative ability of a compound of the invention to inhibit oxidation.

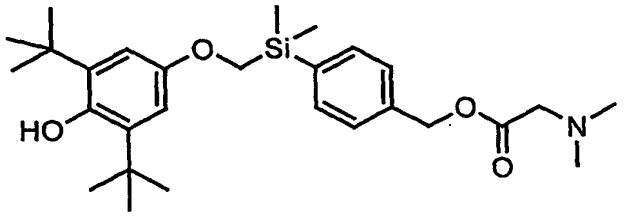
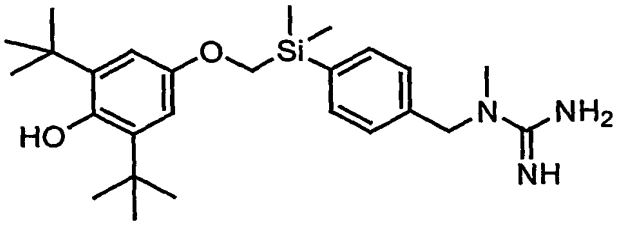
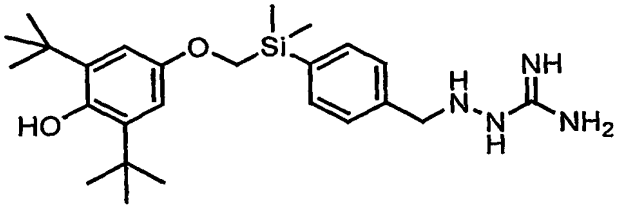
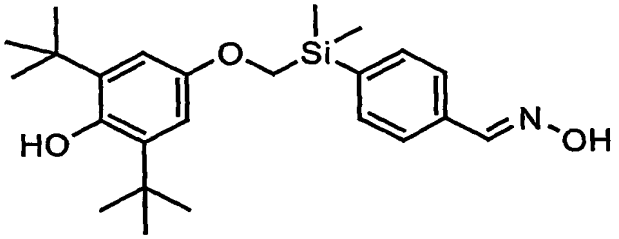
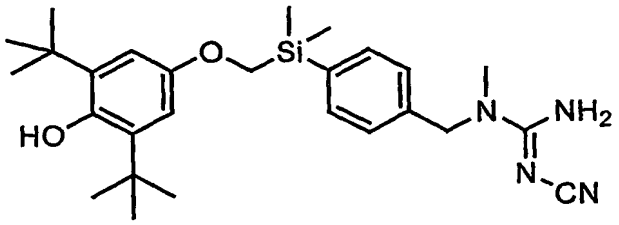
TBARS may be measured as follows: Rabbit serum (Hb 9.16 mg/dl) is purchased from Equitech-Bio, Inc. (Kerrville, TX) and received as frozen 50 mL aliquots. Serum is thawed upon arrival, separated into 5.0 mL aliquots and stored at –20 °C until use. At assay, 1.68 µl of 5 mM compound (in DMSO) is diluted into 1.6

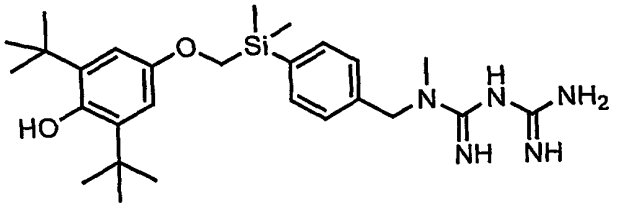
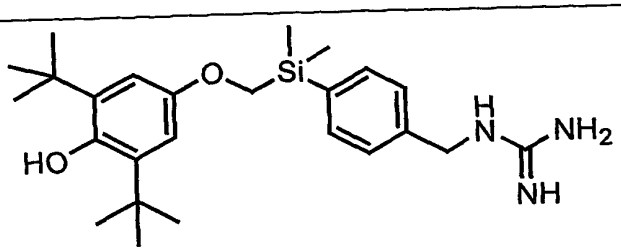
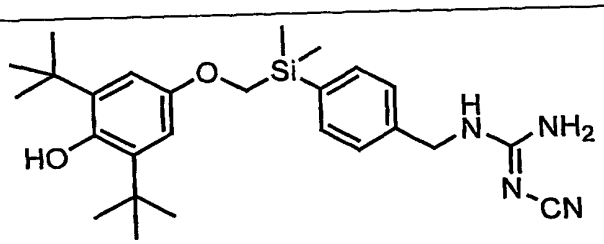
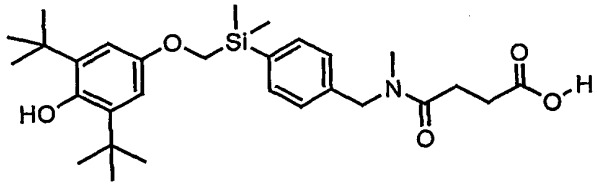
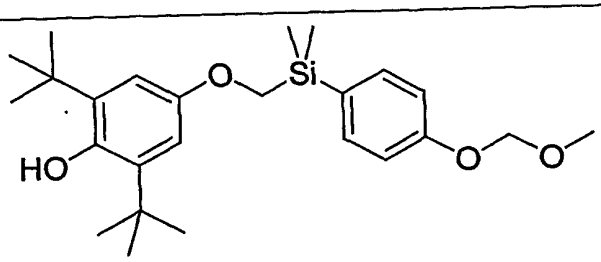
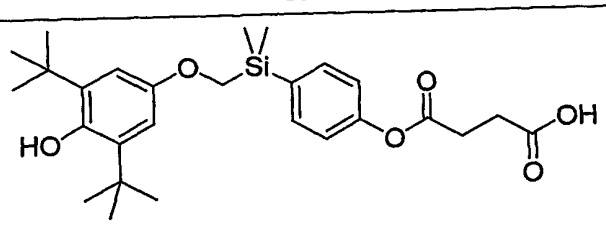
mL thawed rabbit serum contained in round bottom glass flasks. Mixtures are spiked with 80 uL of 100 mM $CuSO_4$ and vortexed briefly to bring $CuSO_4$ into solution. Flasks are open to the atmosphere, suspended in a 37 °C water bath, and stirred at low speed to promote oxidation and mixing of the compound. Care is taken to limit light exposure for the duration of the assay.

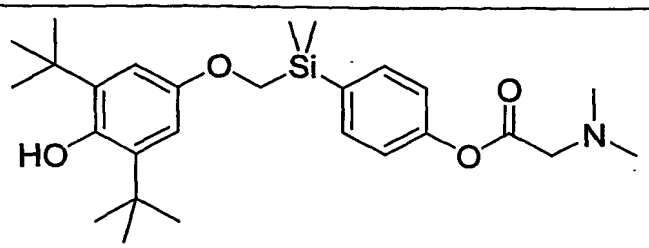
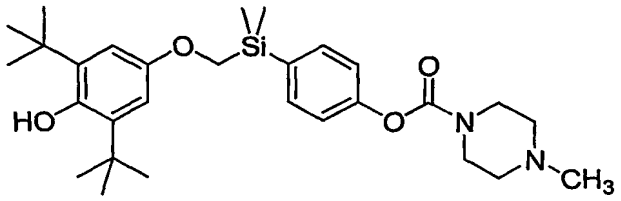
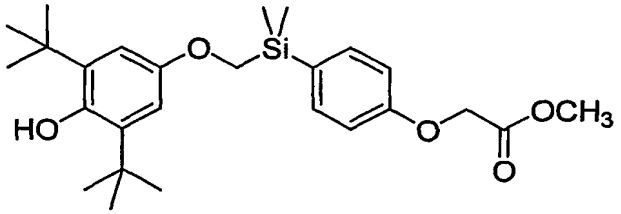
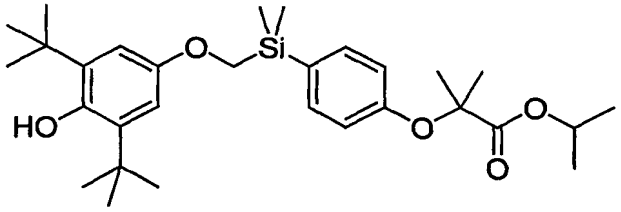
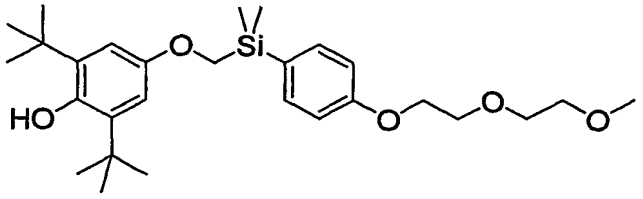
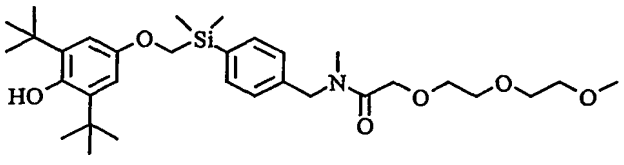
At time zero and subsequent time points thereafter, 26.5 uL aliquots are removed from flasks and transferred to polypropylene Eppendorf tubes where they are precipitated with 250 uL 20% (w/v) TCA, vortexed, and stored in the dark at 4 °C. Once all samples have been collected, 25 uL of a 10% SDS solution is added, samples are again vortexed, and then centrifuged at 13,200 rpm for 5 minutes to pellet debris. Supernatants are transferred to fresh polypropylene Eppendorf tubes and mixed with 250 uL 0.67% TBA in 0.05 N NaOH. Samples are then incubated at 85 °C for 45 minutes, cooled to room temperature, and centrifuged to pellet any remaining debris. Two hundred microliters of resulting supernatants are transferred to clear bottom 96-well plates and absorbance read at 540 nm.

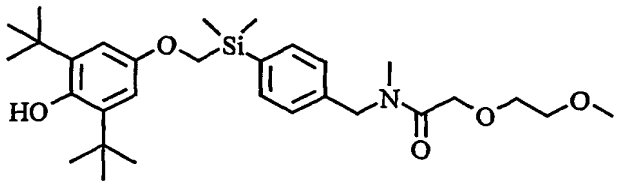
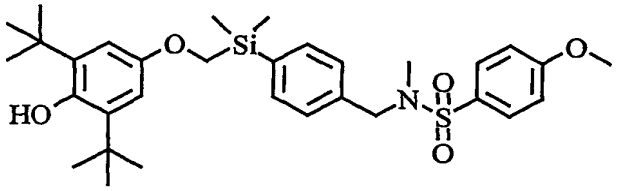
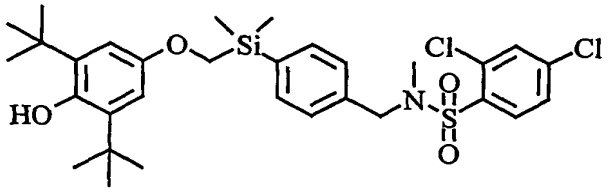
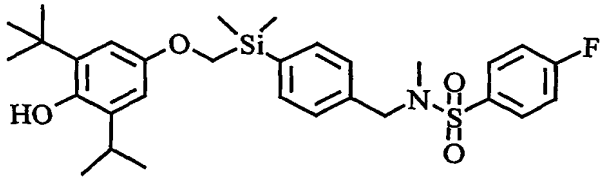
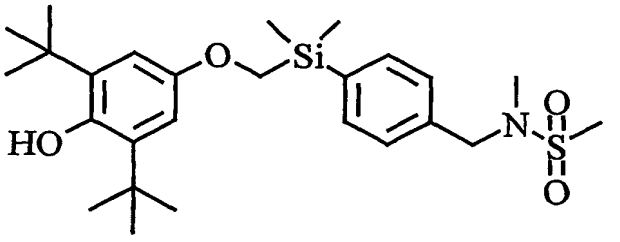
TBARS values for certain preferred compounds of the invention are shown in the table below ($\Delta t_{1/2}$ = $t_{1/2\ (cmpd)} - t_{1/2\ (DMSO)}$: $t_{1/2}$ is the time at which TBARS formation is one-half maximal):

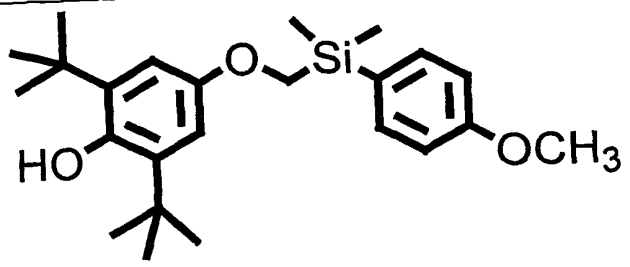
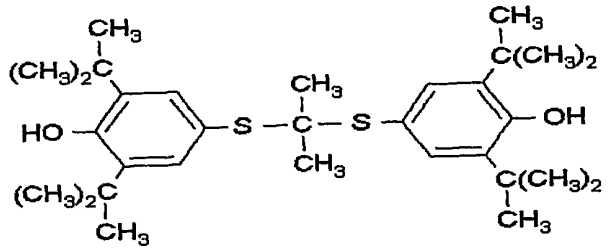
STRUCTURE	TBARS ($\Delta t_{1/2}$) h
 C1	2.95
 C2	3.85

 **C3**	5.95
 **C4**	4.19
 **C5**	6.15
 **C6**	2.41
 **C7**	6.15

 **C8**	2.96
 **C9**	2.70
 **C10**	3.91
 **C11**	2.74
 **C12**	6.04
 **C13**	4.14

 **C14**	2.58
 **C15**	6.55
 **C16**	2.66
 **C17**	3.56
 **C18**	1.75
 **C19**	0.61

 **C20**	1.33
 **C21**	3.74
 **C22**	2.18
 **C23**	1.58
 **C24**	0.21

 C25	4.16
 Probucol	0.75

Alternatively, TBARS values may also be determined as follows. 100 ul of serum is mixed with 400 ul of a 5 mM $CuSO_4$ solution and incubated at 37 °C for 3 hr. The reactions are stopped by addition of 1.0 mL of 20% trichloroacetic acid. Then 1.0 mL of 0.067% thiobarbituric acid in 0.05 N sodium hydroxide is added, mixed, and the samples incubated for 30 min at 90 °C. Samples are centrifuged briefly to pellet undissolved material, and the supernatants are transferred to a 96-well microtiter plate. Absorbances are measured at 540 nm using a microplate reader. The nmoles of MDA produced are calculated form a standard curve of 1 to 10 nmoles of MDA prepared from malonaldehyde bis(dimethylacetal). Serum samples from treated rates are compared to serum samples from control rats.

TBARS values for certain compounds of the invention are shown in the table below:

Compound No.	TBARS (Percent of Control)
26	38%
27	ND
31	17%
47	28%
50	75%
63	70%
75	60%
34	35%
36	32%, 18%
55	57%
66	79%
74	19%
103	49%
80	42%
88	68%
92	70%
104	68%
105	89%
106	49%
107	76%

In a particular example, an *in vivo* study lasting 70 days in which preferred compounds are administered to rabbits *via* their feed, the compounds of the invention are shown to prolong the lag phase for copper-induced lipid peroxidation of serum lipids in a dose-dependent manner. As shown in Figure 1, the increases in lag phase are proportional to serum concentration of a preferred t-butyl phenol compound of Formula III, AC3056. Increased antioxidant activity in serum is also observed in rats fed a diet containing AC3056 where a mean serum concentration of 17.7 μg/mL is achieved.

Example 2: Inhibition of Cytokine-Induced VCAM-1 Expression

Compounds of the present invention are also shown to inhibit cytokine-induced expression of VCAM-1 in cultured human vascular cells. In human coronary artery smooth muscle cells (CASMC), interleukin-4 (IL-4, 100 nmol/L) increases cell surface VCAM-1 to 538% of control. As shown in Figure 2, compounds of the invention inhibit this IL-4 induced VCAM-1 expression in a dose-dependent manner, with half maximal inhibition observed at about 10 μmol/L. Probucol is generally less effective than compounds of the invention in this system (Figure 2).

Similarly, compounds of the present invention are shown to inhibit cytokine-induced (for example, tumor necrosis factor-α (TNF-α)) increases in VCAM-1 expression in human umbilical vein endothelial cells (HUVEC), whereas probucol is generally not effective at similar concentration ranges (Figure 2). The overall effect of the compounds of the present invention on cytokine-induced VCAM-1 expression appears to be relatively selective to this class of adhesion molecule, as evidenced by the significantly higher concentrations of the compound that are required to inhibit cytokine-induced expression of intercellular adhesion molecule-1 (ICAM-1) (IC_{50} >100 μmol/L).

Example 3: Effects on Carbachol-Induced Vascular Dilation

The effect of compounds of the present invention on carbachol-induced vasodilation (endothelium-dependent increase in peripheral conductance) is investigated in cholesterol-fed atherosclerotic rabbits. Cholesterol-feeding will suppress carbachol-induced vasodilation when compared to naive animals fed a

cholesterol-free diet. As shown in Figure 3, treatment of cholesterol-fed rabbits with the compounds of the invention at 300 mg/day for 70 days is shown to prevent the loss of vasodilator action of carbachol. This suggests that the compounds of the invention improve endothelial function in animals exposed to a high cholesterol/high fat diet.

Example 4: Effect on NO Activity Caused by TNF-α in Porcine Aortic Endothelial Cells

The compounds of the present invention are also shown to prevent the loss of NO activity caused by tumor necrosis factor alpha (TNF-α). For example, compounds of the invention prevent the loss of NO activity caused by TNF-α in porcine aortic endothelial cells in culture stimulated with the Ca^{2+}-selective ionophore. NO activity is measured as an increase in cyclic guanosine monophosphate (cGMP) concentration. As shown in Figure 4, inhibition of NO activity by 1 ng/mL TNF-α is blocked by 4 μg/mL (10 μmol/L) of a preferred compound of the invention.

Example 5: Induced Expression of Heme Oxygenase-1 (HMOX-1)

The compounds of the present invention are also shown to induce the expression of HMOX-1. More particularly, compounds of the invention are investigated for influence on gene expression using any number of methodologies known in the art including whole blood nucleic acid extraction and purification followed by QPCR. For example, as shown in Figures 5 and 6, compounds of the invention induce expression of HMOX-1 in unstimulated whole blood and LPS stimulated (1 ng/mL) whole blood over 6 hours at concentrations of 10 and 50 ug/mL.

Example 6: Modulation of Inflammation and Response to Vascular Injury

The compounds of the present invention are shown to influence neointimal thickening after experimental vascular injury. More particularly, compounds of the invention can be investigated to determine their effect on inhibition of leukocyte recruitment, cellular proliferation, and neointimal thickening after murine carotid injury in the murine model of mechanical injury described below.

A murine model of mechanical injury designed to achieve complete endothelial denudation as well as controlled arterial stretching based on the air-drying rat model of Fishman *et al.*, *Lab Invest.*, 32:339-351 (1975) is utilized to investigate the effects of the compounds of the invention. This mouse model shares much in common with widely studied and characterized experimental models of vascular injury, and takes advantage of the genetic diversity of the murine system. It is fundamentally different from previously reported murine models of arterial injury, including endovascular wire scraping (Lindner *et al.*, *Circ Res.*, 73:792-796 (1993)), perivascular cuffing (Moroi *et al.*, *J Clin Invest.*, 101:1225-1232 (1998)), ipsilateral carotid artery ligation (Kumar *et al.*, *Arterioscler Thromb Vasc Biol.*, 17:2238-2244 (1997)), and electrical- (Carmeliet *et al.*, *Am J Pathol.*, 150:761-776 (1997)) or Rose Bengal/green light- (Kikuchi *et al.*, *Atrioscler Thromb Vasc Bio.*, 18:1069-1078 (1998)) induced injury in its ability to reliably achieve both endothelial and medial injury via an endovascular approach resulting in progressive intimal thickening over time.

In the present murine model, intimal and medial thickening are accompanied by progressive vessel enlargement or "positive remodeling" as determined by external elastic lamina radius measurements in uninjured and 28d post-injury vessels. Furthermore, enhanced neointimal thickening is evident when mechanical injury is performed on an atherosclerotic background using Apo E-deficient (Apo $E^{-/-}$) mice fed a high fat diet supplemented with 1.25% cholesterol for 12 weeks. Inflammatory cells are an important component of this neointimal, comprising 34% of total cells at 28d.

The murine model (described above) of endothelial denudation and carotid artery dilation in Apo $E^{-/-}$ male mice fed a high fat diet supplemented with 1.25% cholesterol for 12 weeks is utilized as follows. A breeding colony of C57Bl/6J Apo $E^{-/-}$ mice in a pathogen-free barrier is established, and the mice of the colony receive a compound of the present invention, or vehicle control 18 hours prior to and daily after injury. At Days 1, 3, 7, and 28 post-vascular injury, anesthesia is administered, the chest cavity opened, and the animals sacrificed by right arterial exsanguination. A 22-gauge butterfly catheter is inserted into the left ventricle for *in situ* pressure perfusion at 100 mm Hg with 0.9% saline for 1 min followed by fixation with 4%

paraformaldehyde in 0.1 M phosphate buffer, pH 7.3, for ten minutes. The right and left common carotid arteries are excised and immersed in buffered paraformaldehyde. Spleen and small intestine from three compound-treated and control animals are also harvested as control tissues for immunohistochemistry. All animals preferably receive BrdU, 50 mg/kg i.p., 18 h and 1 h before sacrifice.

Carotid arteries are embedded and two cross sections cut 500 μm apart. The cross section are then stained with hematoxylin and eosin and Verhoeff tissue elastin stain. A histologist blinded to the animal genotype or drug treatment then measures the lumen, intimal, and medial areas of each cross-sectional plane using a microscope equipped with a CCD camera interfaced to a computer running NIH Image v1.60 software. Results for the two planes of each artery are averaged. For immunohistochemistry, standard avidin-biotin procedures for mouse CD45 (leukocyte common antigen, Pharmigen), MOMA-2 (murine macrophages, Serotec) BrdU (DAKO), and SMC actin (DAKO) are used. Immunostained sections are quantified as the percent positivity (number of immunostained positive cells for relevant antigen/total number of nuclei).

To assess effect of a compound of the invention on luminal platelet and leukocyte adhesion to the vessel wall, additional animals are prepared for scanning electron microscopy 1d after injury. Vascular injury and tissue harvesting in these mice are performed as above except modified Ito-Karovsky fixative may be used for perfusion and immersion fixation. Tissues are then rinsed overnight in 0.1M cacodylate buffer at 4 °C, undergo critical drying and sputter coating with gold, and then are imaged on a Cambridge Instruments StereoScan 240.

For example, Figure 7(a) illustrates exemplary quantitative morphometry and Figure 7(b) illustrates exemplary intimal-to-medial ratio in the model of mechanical injury in Apo $E^{-/-}$ male mice that are fed a high fat diet supplemented with 1.25% cholesterol for 12 weeks prior to injury. Test mice receive a preferred t-butyl phenol compound of the invention (AC3056) or a vehicle control 18 hours prior to and daily after injury for 28 days. IEL = internal elastic lamina; EEL = external elastic lamina; I/M = intimal-to-medial ratio; NS = not significant. As shown in Figures 7(a) and 7(b), the compounds of the present invention influence neointimal thickening following experimental vascular injury in that the average neointimal thickness is

reduced, the average lumen thickness is increased, and the intimal/medial ratio is reduced.

Figure 8 illustrates exemplary percent CD45 positive cells (number of immunostained positive cells for CD45/total number of nuclei) in neointima and media of carotid arteries in a model of mechanical injury in Apo $E^{-/-}$ male mice that are fed a high fat diet supplemented with 1.25% cholesterol for 12 weeks prior to injury. Again, test mice receive a t-butyl phenol compound of the invention (AC3056) or a vehicle control 18 hours prior to and daily after injury for 28 days. NS = not significant. As shown in Figure 8, the compounds of the present invention inhibit leukocyte recruitment to the neointimal space following vascular injury.

Figure 9 illustrates exemplary percent Brdu positive cells (number of immunostained positive cells for Brdu/total number of nuclei) in neointima and media of carotid arteries in a model of mechanical injury in Apo $E^{-/-}$ male mice that are fed a high fat diet supplemented with 1.25% cholesterol for 12 weeks prior to injury. Again, test mice receive a preferred t-butyl phenol compound of the invention (AC3056) or a vehicle control 18 hours prior to and daily after injury for 28 days. NS = not significant.

The pharmacology data provide evidence that the compounds of the present invention act as potent antioxidants with anti-atherosclerotic properties. The compounds also lower total and LDL cholesterol concentrations in rabbits, decrease VCAM-1 expression and increase HMOX-1 expression in human vascular cells, as well as reduce neointimal thickening and inhibit lymphocyte recruitment following experimental vascular injury. Thus, the compounds of the present invention have clinical utility in the treatment of vascular access dysfunction.

Example 7: Prevention and Reversal of Erectile Dysfunction in Male Rats

Male Sprague-Dawley rats are used as a model for the study of diabetic erectile dysfunction. Insulin-independent diabetes is induced in 12 week-old rats by a single injection of streptozotocin (40mg/kg i.p.) dissolved in 0.1 M citric acid / trisodium citrate buffer (pH 4 – 4.5). This low dose of streptozotocin has been shown to increase blood glucose while not significantly affecting testosterone levels. Control (non-diabetic) animals receive the equivalent volume of citrate buffer. After one week, tail blood samples are obtained and glucose concentration is measured using an

Acccutrend® glucometer (Boehringer Mannheim, Germany). Diabetes induction is considered successful when glycemia is higher than 200 mg/dl (11 mM).

Erectile response to cavernosal nerve stimulation is conducted in rats anesthetized with ketamine (60 mg/kg) and diazepam (4mg/kg). The surgical procedure consists of dissection and isolation of the right cavernous nerve through an abdominal midline incision and exposure of penile cura through a transverse perineal incision (CNES). Intracavernosal pressure (ICP) measurements are accomplished by insertion into the right crus of a 23-gauge needle connected to a disposable pressure transducer (Abbott, Sligo, Ireland) and a data acquisition system (AD Instruments, Castle Hill, Australia). Left carotid artery and right external jugular vein are catheterized for constant blood pressure measurement and saline infusion, respectively. Electrical stimulation is applied by a delicate platinum bipolar hook electrode connected to a stimulator and current amplifier (Cribertec CS-9, Madrid, Spain). Parameters of electrical stimulation consist of pulses with a duration of 1 ms and 1.5 mA of current intensity for 1 minute. Frequency-response curves are performed by applying stimulation at 1,3 and 10 Hz at 3 minute intervals.

Erectile responses to rat cavernosal nerve stimulation are determined by measuring the peak ICP increase normalized by mean arterial pressure (MAP) values, and area under the curve (AUC) of the ICP increases is normalized by MAP values. The complete frequency response curves are compared by a two-factor ANOVA test.

The representative t-butyl phenol compound is orally administered by preparing rat chow containing 0.3% of the compound dissolved in corn oil. Rats have free access to this chow. The rats included in the preventive treatment group receive the representative compound from the start of the induction of the diabetic state, and erectile responses are determined 8 weeks later. Diabetic control animals are fed with normal rat chow supplemented with corn oil for the 8 week period. The rats included in the restorative treatment group receive normal chow for the initial 8 weeks of diabetes and chow containing 0.3% of a representative compound of the invention for 4 additional weeks. Diabetic control animals for restorative treatments are fed with normal rat chow supplemented with corn oil for 12 weeks.

Induction of diabetes with streptozotocin causes a sustained increase of blood glucose concentration in rats, which is maintained through the duration of the study.

Figures 10 and 11 show that the treatment with 0.3% of the compound, whether preventive or restorative, does not modify glycemia levels.

The effects of preventative treatment with a representative compound of the invention on cardiovascular parameters and erectile responses are measured eight weeks after diabetic induction with streptozotocin. Eight weeks of diabetes do not alter MAP levels in diabetic rats (Figure 12A). There is a significant reduction of heart rate in diabetic rats. This effect is partially prevented by treatment with a compound of the invention (Figure 12B).

Preventative treatment with a compound of the invention significantly improves erectile responses in diabetic rats. Diabetic rats treated with a representative compound of the invention show increased erectile responses when compared with untreated diabetic rats. This potentiating effect is significant when responses are expressed as the AUC of the ICP response to cavernosal nerve stimulation (Figure 13), and is also significant when responses are expressed as the peak increase of ICP after each stimulation (Figure 14).

The effects of restorative treatment with compounds of the invention on cardiovascular parameters and erectile responses is measured twelve weeks after diabetic induction with streptozotocin. Twelve weeks of diabetic induction does not alter MAP levels. Restorative treatment with a representative compound of the invention does not modify MAP levels in diabetic rats (Figure 15A). There is a significant reduction in the heart rate in diabetic rats. This effect is not altered by restorative treatment with compounds of the invention (Figure 15B).

The restorative treatment with compounds of the invention significantly improves erectile responses in diabetic rats. Diabetic rats treated with a representative compound of the invention for four weeks after eight weeks of untreated diabetes show increased erectile responses when compared with twelve weeks untreated diabetic rats. This potentiating effect is significant when responses are expressed as the AUC of the ICP response to cavernosal nerve stimulation (Figure 16). When responses are expressed as the peak increase of the ICP after cavernosal nerve stimulation, there are no significant differences between untreated diabetic rats and rats treated with a representative compound of the invention (Figure 17).

Example 8: Endothelium Dependent Relaxation of Corpus Cavernosum from Diabetic Patients

Specimens of human corpus cavernosum are obtained from impotent men at the time of penile prosthesis implantation as previously described (Angulo, *et al., J. Pharm. Exp. Ther.*, 295: 586-593 (2000)). Tissues are placed in ice cold M-400 solution (pH 7.4; 400 mOsm/kg. Composition in w/v 4.19% manitol, 0.2% KH_2PO_4, 0.97% $K_2HPO_4 \cdot 3\ H_2O$, 0.11% KCl, and 0.08% $NaHCO_3$) at the time of removal and transported to the laboratory for utilization within 16 hours.

To evaluate the effects on trabecular tissues, strips of human corpus cavernosum are mounted on force transducers in 8 ml organ baths (37° C) containing physiological salt solution continuously bubbled with a 95% O_2 / 5% CO_2 mixture to maintain a pH of 7.4. Strips are contracted with 0.5 μM phenylephrine and relaxation responses are evaluated by cumulative additions of test or vehicle control compounds to the chambers. Transmural electrical stimulation (TES) is applied by means of two electrodes on each side of the tissue connected to a stimulator and current amplifier. Usual parameters of TES will be square pulses of 0.5 ms, during 20 s with the voltage adjusted to obtain a current of 75 mA.

For measurement of acute effects of antioxidant treatment on endothelium-dependent relaxation of human corpus cavernosum, corpus cavernosum strips are contracted with phenylephrine and exposed to cumulative concentrations of acetylcholine. Once a full concentration-response curve is obtained, the tissues are washed extensively and exposed to vehicle or the AC3056 antioxidant (10 uM) for 30 min. Tissues are again contracted and exposed to acetylcholine. (n=6-8 for each group).

Acute effects of antioxidant treatment on relaxation induced by transmural electrical stimulation of nitrergic nerves are measured as follows. Strips treated with guanethidine (10 uM) and atropine (0.1 uM) are contracted and transmural electrical stimulation applied at various frequencies (0.5, 1, 2, 6 and 12 Hz). Tissues are then washed and, for 30 min. exposed to vehicle control or the AC3056 antioxidant. Tissues are contracted again and the frequency-response curve is then repeated. (n=6-8 for each group).

Example 9: Preparation of Compounds of the invention

A Preparation of Benzylalcohol Derivatives:

The following compounds of the invention, and similar compounds may be generally prepared according to **Scheme 1.**

Synthesis of (4-Bromobenzyloxy)(tert-butyl)dimethylsilane(2)

Imidazole (12 g, 0.182 mol) is added to a solution of (4-bromophenyl)methanol (**1**) (17 g, 0.091 mol) in dry CH_2Cl_2 (60 mL) and the reaction is stirred at 0 °C. A solution of TBDMSCl (20.87 g, 0.13 mol) in CH_2Cl_2 (30 mL) is added slowly to the reaction over a period of 30 min. and stirred for another 4 hrs. at the same temperature. The reaction is quenched with water (50 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic layer is washed with saturated aq. $NaHCO_3$ (2x50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified over silica gel column chromatography to yield the pure (4-Bromobenzyloxy)*(tert*-butyl)dimethylsilane (**2**) as colorless oil in 84% (23 g) yield.

(Chloromethyl) 4-(((tert-butyl)dimethylsilyl)benzyloxy)dimethylsilane (3)

Compound (2) (20 g, 0.067 mol) is dissolved in dry THF (70 mL) under N_2 atmosphere and cooled to –78°C using dry-ice and ethanol bath. In a dropping funnel attached to the reaction flask, n-BuLi (62.5 mL of 1.6 M in hexanes, 0.1 mol) is slowly added over a period of 1 hr and the resulting solution is stirred at –78 °C for another 1.5 hr. A solution of chloro(chloromethyl)dimethylsilane (9.7 mL, 0.073 mol) in THF (20 mL) is added slowly over a period of 30 min. and the reaction is stirred for another 2 hr. An aqueous sat. NH_4Cl (100 mL) is added and the reaction is allowed to warm to room temperature. The THF is evaporated in vacuum and the residue is dissolved in EtOAc (200 mL). The organic layer is washed with water (2x50 mL), brine (50 mL), dried (anh. Na_2SO_4), filtered and evaporated. The product is purified by silica gel column using 5% EtOAc/Hexanes as eluents. The pure product is obtained as a colorless oil in 86% (19 gm) yield.

(Iodomethyl) 4-(((tert-butyl)dimethylsilyl)benzyloxy)dimethylsilane (4)

To a stirred solution of (chloromethyl) 4-(((*tert*-butyl)dimethylsilyl) benzyloxy)dimethylsilane (3) (14 g, 0.049 mol) in dry CH_3CN (30 mL), NaI (36.5 g, 0.25 mol) is added and the resulting solution was heated on an oil bath at 70 °C. After

6 hrs, all CH_3CN is removed under reduced pressure and the residue is dissolved in CH_2Cl_2 (100 mL), filtered and washed with CH_2Cl_2 (3x20 mL). The combined organic portions are washed with water (2x50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column with 5% EtOAc/Hexanes as eluents. The pure product is obtained as a pale yellow oil in 97% (20 gm) yield.

2,6-Di-tert-butyl-1,4-bisphenol (5)

The bis-phenol (5) is synthesized from 2,6-di-*tert*-butylcyclohexa-2,5-diene-1,4-dione and Zn/HCl according to the experimental condition described earlier. Purity of the bis-phenol (5) is verified by TLC, dried thoroughly under vacuum and stored under N_2 atmosphere.

4-(((4-(hydroxybenzyl)dimethylsilyl)methoxy)-2,6-di-tert-butylphenol (C1)

Under N_2 atmosphere, Cs_2CO_3 (8.78 g, 0.027 mol) is added to a stirred solution of bis-phenol (5) (5 g, 0.023 mol) in dry DMF (15 mL). The heterogeneous reaction mixture is stirred at 60 °C for 1 hr. A solution of (Iodomethyl) 4-(((*tert*-butyl)dimethylsilyl)benzyloxy)dimethylsilane (4) (11.4 g, 0.027 mol) in DMF (15 mL) is added slowly over a period of 1 hr, and the resulting reaction mixture is stirred at 60 °C for an hour. All the solvents are removed under vacuum and the residue is partitioned between EtOAc (100 mL) and an aqueous sat. NH_4Cl (50 mL) solution. The organic layer is removed and washed thoroughly with water (2x50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column using 5-10% EtOAc/Hexanes as eluents to yield product (6) as semi solid material in *ca.* 85% (13.5 g) purity.

To the above product (13.5 g, *ca.* 85%) dissolved in MeOH (10 mL) is added dry HCl (33.5 mL of 2 M in MeOH, 0.067 mol) and the solution is stirred at 0 °C for 2 hrs. All solvents are removed and the residue is dissolved in EtOAc (150 mL). The organic portions are washed with water (2x50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column with 15-20% EtOAc/Hexanes as eluents. The pure product (**C1**) is obtained as a colorless solid in 73% (6.5 gm) yield in two steps.

^{1}H NMR: ($CDCl_3$, 300MHz) δ; 7.63 (d, J = 4.75 Hz, 2H), 7.39 (d, J = 4.84 Hz, 2H), 6.81 (s, 2H), 4.73 (s, 1H), 4.71 (s, 2H), 3.73 (s, 2H), 1.43 (s, 18H), 0.43 (s, 6H);

Analytical HPLC: (C_{18}, 20-90%CH_3CN in 0.1%TFA/H_2O over 15 min) R_t =11.05;

LCMS: Calculated for $C_{24}H_{36}O_3Si$ = 400.24; Found = 401.2 $[M+H]^+$

The following compounds of the invention, and similar compounds, may be prepared according to **Scheme 2.**

4-((((4-benzyloxycarbonyl)propanoic acid)dimethylsilyl)methoxy)-2,6-di-tert-butylphenol (C2)

To a solution of 4-(((4-(hydroxybenzyl)dimethylsilyl)methoxy)-2,6-di-*tert*-butylphenol (**I**) (0.5 g, 0.0013 mol) in CH_2Cl_2 (5 mL), pyridine (0.32 mL, 0.0038 mol), succinic anhydride (0.15 g, 0.0015 mol) and cat. amount of DMAP(4 mg) are added and the resulting solution is stirred at 0 °C. After 2hrs, the reaction is quenched by adding water (30 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer is separated and washed with water (2x50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column with 2-5% MeOH/ CH_2Cl_2 as eluents. The pure product (**C2**) is obtained as a colorless solid in 80% (0.5 g) yield.

^{1}H NMR: ($CDCl_3$, 300MHz) δ; 7.62 (d, J = 4.80 Hz, 2H), 7.36 (d, J = 4.80 Hz, 2H), 6.80 (s, 2H), 5.15 (s, 2H), 4.75 (s, 1H), 3.73 (s, 2H), 2.70 (m, 4H), 1.43 (s, 18H), 0.43 (s, 6H);

Analytical HPLC: (C_{18}, 20-90%CH_3CN in 0.1% TFA/H_2O over 15 min) R_t =11.16;

LCMS: Calculated for $C_{28}H_{40}O_6Si$ = 500.26; Found = 501.3 $[M+H]^+$

4-(((3,5-di-tert-butyl-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl 2-(dimethyl amino) acetate (C3)

To compound 4-(((4-(hydroxybenzyl)dimethylsilyl)methoxy)-2,6-di-*tert*-butylphenol (**C1**) (0.23 g, 0.575 mmol) dissolved in 4:1 v/v CH_2Cl_2:DMF (5 mL), DMAP (0.07 g, 0.58 mmol), N,N-dimethylglycine hydrochloride (0.121 g, 0.86 mmol) and DCC (0.355 g, 1.73 mmol) are added and the resulting solution is stirred at 0 °C overnight. The reaction is quenched with water (50 mL) and diluted with

CH_2Cl_2 (50 mL). The organic layer is separated, washed with water (2x50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column with 30-60% EtOAc/Hexanes as eluents. The pure product (**C3**) is obtained as a fluffy colorless solid in 89% (0.25 g) yield.

^{1}H NMR: ($CDCl_3$, 300MHz) δ; 7.62 (d, J = 4.79 Hz, 2H), 7.37 (d, J = 4.80 Hz, 2H), 6.80 (s, 2H), 5.18 (s, 2H), 4.75 (s, 1H), 3.73 (s, 2H), 3.23 (s, 2H), 2.37 (s, 6H), 1.43 (s, 18H), 0.42 (s, 6H);

Analytical HPLC: (C_{18}, 20-90% CH_3CN in 0.1% TFA/H_2O over 15 min) R_t =9.42;

LCMS: Calculated for $C_{28}H_{43}NO_4Si$ = 485.3; Found = 486.3 $[M+H]^+$

B. Preparation of Benzylamine Derivatives

The following compounds of the invention, and similar compounds, may be prepared according to **Scheme 3.**

4-(((3,5-di-tert-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl methanesulfonate (7)

Under N_2 atmosphere, to a stirred solution of alcohol (**I**) (4.2 g, 0.0105 mol) in dry CH_2Cl_2 (10 mL) at 0 °C, Et_3N (4.4 mL, 0.031 mol) and DMAP (0.256 g, 0.0021 mol) are added. A solution of $MeSO_2Cl$ (1.26 mL, 0.0158 mol) in dry CH_2Cl_2 (5 mL) is added slowly over a period of 10 min and stirred for another 2 hrs. The reaction is diluted with CH_2Cl_2 (50 mL) and quenched with water (20 mL). The organic layer is separated and washed with water (2x50 mL), brine (50 mL), dried (anh. Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column with 5 % EtOAc/Hexanes as eluents. The pure mesylated product (7) is obtained as fluffy colorless solid in 80% (4.0 g) yield.

LCMS: Calculated for $C_{25}H_{38}O_5SSi$ = 478.22; Found = 479.3 $[M+H]^+$

4-(((4-azidomethyl)phenyl)dimethylsilyl)methoxy)-2,6-di-tert-butylphenol (8)

The mesylate (7) (3 g, 0.0063 mol) is dissolved in CH_3CN (10 mL) and NaN_3 (1.63 g, 0.0251 mol) was added. The heterogeneous reaction mixture is heated on an oil bath at 80 °C for 6 hrs. All solvents are removed and dried. The residue is dissolved in CH_2Cl_2 (50 mL), filtered and repeatedly washed with CH_2Cl_2 (5x20mL). The combined organic portions are washed with water (2x50 mL), brine (50 mL),

dried (anhydrous Na_2SO_4), filtered and evaporated. The crude azido compound is purified on a silica gel column using 5-10% EtOAc/hexanes as eluents. The pure material (8) is obtained as a colorless solid in 96% (2.55 g) yield.

LCMS: Calculated for $C_{24}H_{35}N_3O_2Si$ = 425.25; Found = 426.2 $[M+H]^+$

4-(((4-aminomethyl)phenyl)dimethylsilyl)methoxy)-2,6-di-tert-butylphenol (9)

To a solution of the azido compound (8) (2.2 g, 0.052 mol) in 5% H_2O in THF (10 mL), triphenylphosphine (1.63 g, 0.0062 mol) is added and the resulting solution is initially stirred for 2 hrs at 0 °C and later to room temperature overnight. All solvents are removed in vacuum and the residue is directly loaded into silica gel column and eluted using 50-90% EtOAc/Hexanes to remove all non-polar impurities and later with 5-10% MeOH/ CH_2Cl_2 to isolate the product. The pure amine (9) is obtained as a colorless fluffy solid in 95% (1.95 g) yield.

LCMS: Calculated for $C_{24}H_{37}NO_2Si$ = 399.26; Found = 400.2 $[M+H]^+$

(4-(((3,5-di-tert-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)(N,N,di-tert-butyloxycarbonyl)guanidine (11)

The amine (9) (0.6 g, 0.0015 mol), DMF (10 mL) and Et_3N (0.62 mL, 0.0045 mol) are taken in a flask under N_2 atmosphere and cat. amounts of $HgCl_2$ (20 mg) is added followed by the 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (10) (0.654 g, 0.0023 mol). The heterogeneous reaction is stirred for 4 hrs. The reaction is quenched with H_2O (20 mL) and DMF is removed under vacuum. The residue is filtered and washed repeatedly with CH_2Cl_2 (4x10 mL). The combined organic portions are washed with water (50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column using 5-10% EtOAc/Hexanes as eluents. The pure guanidine derivative (11) is obtained as a white solid in 94% (0.9 g) yield.

LCMS: Calculated for $C_{35}H_{55}N_3O_6Si$ = 641.39; Found = 642.4 $[M+H]^+$

(4-(((3,5-di-tert-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)guanidine (C9)

To a stirred solution of compound (11) (0.45 g, 0.72 mmol) in CH_2Cl_2 (2 mL) at 0 °C, is added TFA (2.8 mL, 0.014 mol) and the solution is stirred at 0 °C for 2 hrs. All solvents are removed under vacuum and the residue is dissolved in CH_2Cl_2 (30 mL). The organic portion is washed with aqueous sat. $NaHCO_3$ (2x20 mL), water

(2x50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column using 5-10% MeOH/CH_2Cl_2 as eluents. The pure guanidine (**C9**) is obtained as a colorless fluffy solid in 86% (0.26 g) yield.

^{1}H NMR: ($CDCl_3$, 300MHz) δ; 8.36 (m, 1H), 7.60 (d, J = 4.76 Hz, 2H), 7.24 (d, J = 4.73 Hz, 2H), 6.79 (s, 2H), 4.74 (s, 1H), 4.27 (d, J = 3.48 Hz, 2H), 3.72 (s, 2H), 1.41 (s, 18H), 0.40 (s, 6H);

Analytical HPLC: (C_{18}, 15-90% CH_3CN in 0.1% TFA/H_2O over 15 min) R_t = 9.39;

LCMS: Calculated for $C_{25}H_{39}N_3O_2Si$ = 441.28; Found = 442.2 $[M+H]^+$

The following compounds of the invention, and similar compounds, may be prepared according to **Scheme 4**.

(4-(((3,5-di-tert-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)2-cyanoguanidine (C10)

The amine hydrochloride (12) (0.45 g, 1 mmol) (prepared from the corresponding amine using dry HCl/MeOH and drying in vacuum) and sodium dicyanamide (0.12 g, 1.34 mmol) is dissolved in 5% H_2O in iPrOH (5 mL). The solution is thoroughly flushed with N_2 and heated in a sealed tube at 120°C for 5 hrs. After cooling to room temperature, all solvents are removed under vacuum and the residue is dissolved in EtOAc (50 mL). The organic portion is washed with aqueous sat. NH_4Cl (2x20 mL), water (2x20 mL), brine (30 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column using 5-10% MeOH/CH_2Cl_2 as eluents. The pure product (**C10**) is obtained as a colorless fluffy solid in 62% (0.3 g) yield.

^{1}H NMR: ($CDCl_3$, 300MHz) δ; 7.60 (d, J = 4.67 Hz, 2H), 7.26 (d, J = 4.62 Hz, 2H), 6.79 (s, 2H), 5.18 (bd, s, 2H), 4.75 (s, 1H), 4.35 (d, J = 3.38 Hz, 2H), 3.72 (s, 2H), 1.40 (s, 18H), 0.41 (s, 6H);

Analytical HPLC: (C_{18}, 15-90%CH_3CN in 0.1% TFA/H_2O over 15 min) R_t =10.52;

LCMS: Calculated for $C_{26}H_{38}N_4O_2Si$ = 466.28; Found = 467.3 $[M+H]^+$

(Chloromethyl)(4-(diethoxymethyl)phenyl)dimethylsilane (14)

Compound (13) (25 g, 0.097 mol) is dissolved in dry THF (70 mL) under N_2 atmosphere and cooled to –78 °C using a dry-ice/ethanol bath. In a dropping funnel

attached to the reaction flask, n-BuLi (121.1 mL of 1.6 M in hexanes, 0.195 mol) is slowly added over a period of 1 hr and the resulting solution is stirred at –78 °C for another 1.5 hr. A solution of chloro(chloromethyl)dimethylsilane (16.6 mL, 0.116 mol) in THF (10 mL) is added slowly over a period of 30 min. and the reaction is stirred for an additional 2 hrs at –78 °C. An aqueous sat. NH_4Cl (100 mL) is added and the reaction is allowed to warm to room temperature. The THF is evaporated in vacuum and the residue is dissolved in EtOAc (200 mL). The organic layer is washed with water (2x50 mL), brine (50 mL), dried (anh. Na_2SO_4), filtered and evaporated. The product is purified by silica gel column using 3-10% EtOAc/Hexanes as eluents. The pure product (14) is obtained as a colorless oil in 65% (18 gm) yield.

The following compounds of the invention, and similar compounds, may be prepared according to **Scheme 5**.

(Iodomethyl)(4-(diethoxymethyl)phenyl)dimethylsilane (15)

To a stirred solution of (chloromethyl)(4-(diethoxymethyl)phenyl) dimethylsilane (14) (19 g, 0.066 mol) in dry CH_3CN (30 mL), NaI (49.5 g, 0.33 mol) is added and the resulting solution is heated on an oil bath to 70 °C. After 6 hrs, all CH_3CN is removed under reduced pressure and the residue is dissolved in CH_2Cl_2 (100 mL), filtered and washed with CH_2Cl_2 (3x20 mL). The combined organic portions are washed with water (2x50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column with 5% EtOAc/Hexanes as eluents. The pure iodo product (15) is obtained as pale yellow oil in 96% (24 gm) yield.

4-(((3,5-di-tert-butyl-4-hydroxyphenoxy)methyl)dimethylsilyl)benzaldehyde (17)

Under N_2 atmosphere, Cs_2CO_3 (10.54 g, 0.032 mol) is added to a stirred solution of bis-phenol (5) (6 g, 0.027 mol) in dry DMF (15 mL) and the heterogeneous reaction mixture is stirred at 60°C for 1 hr. A solution of (Iodomethyl)(4-(diethoxymethyl)phenyl)dimethylsilane (15) (12.55 g, 0.032 mol) in DMF (5 mL) is added slowly over a period of 1 hr, and the resulting reaction mixture is stirred at 60 °C for an hour. All the solvents are removed under vacuum and the residue is partitioned between EtOAc 100 mL) and an aqueous NH_4Cl (50 mL) solution. The organic layer is removed and washed thoroughly with water (2x50 mL),

brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column using 5-10% EtOAc/Hexanes as eluents to isolate the product (16) in *ca.* 94% (13.5 g) purity.

To the above mixture (13.5 g, *ca.* 94% pure in MeOH (15 mL) is added dry HCl (85 mL of 2 M in MeOH, 0.17 mol) and the resulting solution is stirred at 0 °C for 12 hr. All solvents are removed and the residue is dissolved in EtOAc (150 mL). The organic portions are washed with water (2x50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column with 15-20% EtOAc/Hexanes as eluents. The pure product (17) is obtained as a colorless solid in 71% (7.6 g).

LCMS: Calculated for $C_{24}H_{34}O_3Si$ = 398.23; Found = 399.2[M+H$^+$]

The following compounds of the invention, and similar compounds, may be prepared according to **Scheme 6.**

*(4-(((3,5-di-tert-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)amino guanidine (**C5**)*

To a chilled (0°C) and stirred solution of aldehyde (17) (0.05 g, 0.126 mol) in MeOH (5 mL) sodium triacetoxyborohydride (0.08 g, 0.377 mol) is added. After 5 minutes, aminoguanidine (0.021 g, 1.88 mmol) is added and stirred at 0°C for 2 hrs and warmed to room temperature overnight. All solvent is removed under vacuum and the residue is dissolved in EtOAc (50 mL) and treated with an aqueous sat. NH_4Cl (50 mL) solution. The organic layer is separated and washed with water (2x50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column using 5% MeOH/ CH_2Cl_2 as eluents. The pure amino guanidine product (**C5**) is obtained as a pale yellow oil in 67% (0.038 gm) yield.

^{1}H NMR: ($CDCl_3$, 300MHz) δ; 7.67 (s, 1H), 7.64 (d, J = 4.73 Hz, 2H), 7.31 (d, J = 4.73 Hz, 2H), 6.80 (s, 2H), 6.37 (bd. S, 2H), 6.04 (bd. S, 2H), 4.75 (s, 1H), 4.23 (t, J = 3.38 HZ, 1H), 3.96 (d, J = 3.4 HZ, 2H), 3.74 (s, 2H), 1.43 (s, 18H), 0.43 (s, 6H);

Analytical HPLC: (C_{18}, 20-90%CH_3CN in 0.1% TFA/H_2O over 15 min) R_t = 9.18;

LCMS: Calculated for $C_{25}H_{40}N_4O_2Si$ = 456.29; Found = 457.3 [M+H]$^+$

(4-(((3,5-di-tert-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)N-hydroxyaminobenzylidene (C6)

To a chilled (0°C) and a stirred solution of aldehyde (17) (0.05 g, 0.126 mol) in MeOH (5 mL) sodium triacetoxyborohydride (0.08 g, 3.77 mmol) is added. After 5 minutes, hydroxylamine hydrochloride (0.013 g, 1.88 mmol) is added and stirred at 0°C for 2 hrs and warmed to room temperature overnight. All the solvent is removed under vacuum and the residue is dissolved in EtOAc (50 mL) and treated with an aqueous sat. NH_4Cl (50 mL) solution. The organic layer is separated and washed with water (2x50 mL), brine (50 mL), dried (anh. Na_2SO_4), filtered and evaporated. The product is purified by silica gel column using 2-5% MeOH/ CH_2Cl_2 as eluents. The pure product **(C6)** is obtained as white solid in 60% (0.03 gm) yield.

^{1}H NMR($CDCl_3$, 300MHz) δ; ($CDCl_3$, 300MHz) δ; 8.13 (s, 1H), 7.63 (d, J = 4.85 Hz, 2H), 7.56 (d, J = 4.81 Hz, 2H), 6.79 (s, 2H), 4.73 (s, 1H), 3.73 (s, 2H), 1.43 (s, 18H), 0.43 (s, 6H);

Analytical HPLC: (C_{18}15-90% CH_3CN in 0.1%TFA/H_2O over 15 min) R_t =11.41;

LCMS: Calculated for $C_{24}H_{35}NO_3Si$ = 413.24; Found = 414.2 $[M+H]^+$

C. Preparation of N-Methylbenzylamine Derivatives

The following compounds of the invention, and similar compounds, may be prepared according to **Scheme 7.**

4-((dimethyl(4-((methylamino)methyl)phenyl)silyl)methoxy)-2,6-di-tert-butylphenol (18)

To a chilled (0°C) and stirred solution of aldehyde (17) (4.0 g, 0.010 mol) in MeOH (20 mL) sodium triacetoxyborohydride (6.36 g, 0.030 mol) is added and stirred at 0°C. After 5 minutes, methylamine hydrochloride (1.02 g, 0.015 mol) is added and allowed to stir at 0°C for 2 hrs and to room temperature overnight. All the solvent is removed under vacuum and the residue is dissolved in EtOAc (100 mL) and treated with an aqueous sat. NH_4Cl (50 mL) solution. The organic layer is separated and washed with water (2x50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The product is purified by silica gel column using 5-10% MeOH/

CH_2Cl_2 as eluents. The pure methylamine derivative (18) is obtained as pale a purple fluffy solid in 95% (3.95 gm) yield.

LCMS: Calculated for $C_{25}H_{39}NO_2Si$ = 413.28; Found = 414.2 $[M+H]^+$

(4-(((3,5-di-tert-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)(1,3-bis(tert-butyoxycarbonyl) (methyl)guanidine (19)

To a solution of the amine (18) (0.5 g, 1.21 mmol), DMF (10 mL) and Et_3N (0.49 mL, 3.63 mmol) under a N_2 atmosphere are added cat. amounts of HgCl2 (20 mg) followed by 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (10) (0.53 g, 1.82 mmol). The heterogeneous reaction is stirred for 4 hrs. The reaction is quenched with H_2O (20 mL) and DMF is removed under vacuum. The residue is triturated with CH_2Cl_2 (20 mL), filtered and washed repeatedly with CH_2Cl_2 (4x10 mL). The combined organic portions are washed with water (50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column using 5-10% EtOAc/Hexanes as eluents. The pure product (19) is obtained as a colorless solid in 86% (0.68 g) yield.

LCMS: Calculated for $C_{36}H_{57}N_3O_6Si$ = 655.4; Found = 656.4 $[M+H]^+$

(4-(((3,5-di-tert-4-hydroxyphenoxy) methyl)dimethylsilyl)benzyl)(methyl) guanidine (C4)

To a chilled (0°C) solution of compound (19) (0.45 g, 0.68 mmol) in CH_2Cl_2 (2 mL), TFA (2.8 mL, 0.014 mol) is added and the solution is stirred for 2 hrs. All solvents are removed under vacuum and the remaining residue is dissolved in CH_2Cl_2 (30 mL). The organic portion is washed with an aqueous sat. $NaHCO_3$ (2x20 mL), water (2x50 mL), brine (50 mL), dried (anh. Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column using 5-10% MeOH/CH_2Cl_2 as eluents. The pure product (C4) is obtained as a colorless fluffy solid in 94% (0.29 g) yield.

^{1}H NMR: (5%CD_3OD in $CDCl_3$, 300MHz) δ; 7.61 (d, J = 4.76 Hz, 2H), 7.16 (d, J = 4.80 Hz, 2H), 6.76 (s, 2H), 4.47 (s, 2H), 3.70 (s, 2H), 3.00 (s, 3H), 1.39 (s, 18H), 0.39 (s, 6H);

Analytical HPLC: (C_{18}, 20-90% CH_3CN in 0.1% TFA/H_2O over 15 min) R_t =9.17;

LCMS: Calculated for $C_{26}H_{41}N_3O_2Si$ = 455.3; Found = 456.3 $[M+H]^+$

(4-(((3,5-di-tert-4-hydroxyphenoxy) methyl)dimethylsilyl)benzyl)-2-cyano(methyl)guanidine (C7)

The amine hydrochloride (20) (0.3 g, 0.67 mmol) (prepared from the corresponding amine using dry HCl/MeOH and drying in vacuum) and sodium dicyanamide (0.0773 g, 0.87 mmol) are dissolved in 5% H_2O in iPrOH (5 mL). The solution is thoroughly flushed with N_2 and heated in a sealed tube at 120°C for 5 hrs. After cooling to room temperature, all solvents are removed under vacuum and the residue is dissolved in EtOAc (50 mL). The organic portion is washed with an aqueous sat. NH_4Cl (2x20 mL), water (2x20 mL), brine (30 mL), dried (anh. Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column using 5-10% MeOH/CH_2Cl_2 as eluents. The pure product (**C7**) is obtained as a colorless fluffy solid in 63% (0.2 g) yield.

^{1}H NMR: ($CDCl_3$, 300MHz) δ; 7.61 (d, J = 4.78 Hz, 2H), 7.23 (d, J = 4.82 Hz, 2H), 6.79 (s, 2H), 5.27 (bd. S, 2H), 4.73 (s, 1H), 4.58 (s, 2H), 3.72 (s, 2H), 3.00 (s, 3H), 1.42 (s, 18H), 0.41 (s, 6H);

Analytical HPLC:(C_{18}, 15-90% CH_3CN in 0.1% TFA/H_2O over 15 min) R_t =10.91;

LCMS: Calculated for $C_{27}H_{40}N_4O_2Si$ = 480.29; Found = 481.3 $[M+H]^+$

The following compounds of the invention, and similar compounds, may be prepared according to **Scheme 8**.

(4-(((3,5-di-tert-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)(methyl) biguanidine (C8)

The amine hydrochloride (20) (0.3 g, 0.67 mmol) (prepared from the corresponding amine using dry HCl/MeOH and drying in vacuum) and dicyanadiimide (0.073 g, 0.87 mmol) are dissolved in 5% H_2O in iPrOH (5 mL). The solution is thoroughly flushed with N_2 and heated in a sealed tube at 120°C for 4 hrs. After cooling to room temperature, all solvents are removed under vacuum and the remaining residue is dissolved in EtOAc (50 mL). The organic portion is washed with an aqueous sat. NH_4Cl (2x20 mL), water (20 mL), brine (30 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column using 10-20% MeOH/CH_2Cl_2 as eluents. The pure product (**C8**) is obtained as a colorless fluffy solid in 46% (0.15 g) yield.

^{1}H NMR: (5% CD_3OD in $CDCl_3$, 300MHz) δ; 7.56 (d, J = 4.80 Hz, 2H), 7.18 (d, J = 4.78 Hz, 2H), 6.75 (s, 2H), 4.60 (s, 2H), 3.68 (s, 2H), 2.96 (s, 3H), 1.37 (s, 18H), 0.37 (s, 6H);

Analytical HPLC: (C_{18}, 15-90% CH_3CN in 0.1% TFA/H_2O over 15 min) R_t =9.41;

LCMS: Calculated for $C_{27}H_{43}N_5O_2Si$ = 497.32; Found = 498.3 $[M+H]^+$

3-(N-(4-(((3,5-di-tert-butyl-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)-N-methylcarbamoyl)propanoic acid (C11)

To a solution of amine (18) (0.2 g, 0.484 mmol) in CH_2Cl_2 (5 mL), DMAP (0.059 g, 0.48 mmol) and succinic anhydride (0.058 g, 0.58 mmol) are added and the resulting solution is stirred at 0°C. After 2hrs, the reaction is quenched by adding water (20 mL) and diluted with CH_2Cl_2 (40 mL). The organic layer is separated and washed with water (50 mL), brine (50 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The crude material is purified by silica gel column with 5-10% MeOH/ CH_2Cl_2 as eluents. The pure product (**C11**) is obtained as a colorless solid in 63% (0.15 g) yield.

^{1}H NMR: ($CDCl_3$, 300MHz) (most of the NMR signals are split into two identical sets having intensity ratio of 1:1.4) δ; 7.62 and 7.57 (d, J = 4.73 Hz, 2H), 7.23 and 7.17 (d, J = 4.80 Hz, 2H), 6.79 (s, 2H), 4.75 (bd. s, 1H), 4.60 and 4.56 (s, 2H), 3.73 and 3.71 (s, 2H), 2.99 and 2.97 (s, 3H), 2.73 and 2.71 (m, 4H), 1.42 (s, 18H), 0.41 (s, 6H);

Analytical HPLC: (C_{18}, 15-90% CH_3CN in 0.1% TFA/H_2O over 15 min) R_t =10.8;

LCMS: Calculated for $C_{29}H_{43}NO_5Si$ = 513.29; Found = 514.3 $[M+H]^+$

D. Preparation of Phenolic Derivatives:

The following compounds of the invention, and similar compounds, may be prepared according to **Schemes 9, 10, 11 and 12.**

1-Bromo-4-(methoxymethoxy)benzene (22)

4-Bromophenol (8.65 g, 50 mmol), dimethoxymethane (40 mL, 450 mmol), *p*-tolunesulfonic acid monohydrate (100 mg) are dissolved in 200 mL anhydrous CH_2Cl_2 in a 500-mL Soxhlet extraction apparatus containing 50 g type 3A molecular

sieve, and the solution is refluxed under argon overnight. The reaction mixture is allowed to cool, concentrated under the reduced pressure, and purified through flash chromatography (SiO_2, 3% EtOAc/hexane) to give the desired product (22) as colorless oil (5.78 g, 53%): ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.38 (d, J = 5.4Hz, 2H), 6.92 (d, J = 5.4Hz, 2H), 5.14 (s, 2H), 3.47 (s, 3H).

(Chloromethyl)(4-(methoxymethoxy)phenyl)dimethylsilane (23)

1-Bromo-4-(methoxymethoxy)benzene (22) (9.51 g, 44 mmol) is dissolved in 150 mL anhydrous ethyl ether in a 500-mL round bottom flask, and the solution is cooled down to -78°C. With continuous stirring under argon, 75 mL *tert*-butyl lithium (1.7M in hexane, 127 mmol) is added dropwise through a syringe, and the reaction is kept at -78°C for additional 30 minutes. 18 mL chloro(chloromethyl)dimethylsilane (133 mmol) is dropped carefully into the reaction flask through a syringe, and the reaction mixture is allowed to warm up slowly to room temperature overnight. The reaction is quenched with 100 mL saturated NH_4Cl and the organic layer is separated and dried over anhydrous Na_2SO_4. The solvents are evaporated and the residue is purified by flash chromatography (SiO_2, 3% EtOAc/hexane) to give the desired product (23) as colorless oil (10.57 g, 98%): ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.48 (d, J = 5.1Hz, 2H), 7.06 (d, J = 5.1Hz, 2H), 5.20 (s, 2H), 3.48 (s, 3H), 2.93 (s, 2H), 0.40 (s, 6H).

(Iodomethyl)(4-(methoxymethoxy)phenyl)dimethylsilane (24)

To a 500-mL round bottom flask is charged (chloromethyl)(4-(methoxymethoxy)phenyl)dimethylsilane (23) (10.57 g, 43 mmol), NaI (19.4 g, 130 mmol), 200 mL anhydrous CH_3CN, and the reaction mixture is refluxed under argon overnight. The solution is allowed to cool down to room temperature, and the precipitate that occurred upon cooling is filtered off. The filtrate is evaporated in vacuum and the residue is purified by flash chromatography (SiO_2, 5% EtOAc/hexane) to give the desired product (24) as colorless oil (10.68 g, 74%): ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.47 (d, J = 5.1Hz, 2H), 7.06 (d, J = 5.1Hz, 2H), 5.20 (s, 2H), 3.48 (s, 3H), 2.16 (s, 2H), 0.42 (s, 6H)

4-(((4-(Methoxymethoxy)phenyl)dimethylsilyl)methoxy)-2,6-di-tert-butylphenol (C12)

To a 250-mL flask is added 2,6-di-*tert*-butyl-1,4-bisphenol (5) (6.93 g, 31 mmol), (iodomethyl)(4-(methoxymethoxy)phenyl)dimethylsilane (24) (10.60 g, 31 mmol), Cs_2CO_3 (11.25 g, 35 mmol), anhydrous CH_3CN, and the mixture is stirred at 80°C under steady stream of argon overnight. The reaction is quenched with 50 mL saturated NH_4Cl, and extracted with 100 mL CH_2Cl_2. The organic layer is separated, washed with 100 mL brine, and dried over anhydrous Na_2SO_4. The solvent is evaporated and the residue is purified with flash chromatography (SiO_2, hexane) to afford the desired product (**C12**) as slightly yellow solid (11.35 g, 85%): ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.54 (d, J = 5.1Hz, 2H), 7.06 (d, J = 5.1Hz, 2H), 6.80 (s, 2H), 5.20 (s, 2H), 4.72 (s, 1H), 3.70 (s, 2H), 3.48 (s, 3H), 1.43 (s, 18H), 0.40 (s, 6H); Retention time in RP-HPLC (C_{18}, 30-95% CH_3CN in 0.1% TFA/H_2O over 7 min) is 5.02; Calculated mass for $C_{25}H_{43}O_6Si$ $(M+2H_2O+H)^+$ 467.3, found by LC-MS 467.3; Elemental analysis for $C_{25}H_{38}O_4Si$ clacd: C, 69.72; H, 8.89; O, 14.86; Si, 6.52; found: C, 69.35; H, 8.64; N, 0.20.

4-(((4-Phenol)dimethylsilyl)methoxy)-2,6-di-tert-butylphenol (25)

To a solution of 4-(((4-(methoxymethoxy)phenyl)dimethylsilyl)methoxy)-2,6-di-*tert*-butylphenol (**C12**) (6.23 g, 14 mmol) in 200 mL *p*-dioxane in a 500-mL round bottom flask is added 50 mL 2.0N HCl, and the mixture is stirred under argon at room temperature for 3 days. The solution is extracted with 200 mL EtOAc, and the solvents are evaporated under reduced pressure. The residue is purified by flash chromatography (SiO_2, 5% EtOAc/hexane followed by 10% EtOAc/hexane) to give the desired product (25) as colorless liquid (2.73 g) and the recovered starting material as slight yellow solids (2.70 g). The colorless liquid turned to white solid upon standing at room temperature. The calculated yield is 50%: ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.49 (d, J = 5.1Hz, 2H), 6.86 (d, J = 5.1Hz, 2H), 6.80 (s, 2H), 4.81 (s, 1H), 4.72 (s, 1H), 3.70 (s, 2H), 1.43 (s, 18H), 0.39 (s, 6H); Elemental analysis for $C_{23}H_{34}O_3Si$, calcd: C, 71.46; H, 8.86; O, 12.42; Si, 7.26; found: C, 70.33; H, 8.96; N, 0.08.

Succinic 4-(((3,5-di-tert-butyl-4-hydroxyphenoxy)methyl)dimethylsilyl)phenol ester (C13)

To a 10-mL round bottom flask is added 4-(((4-phenol)dimethylsilyl)methoxy)-2,6-di-*tert*-butylphenol (25) (0.150 g, 0.388 mmol),

succinic anhydride (0.388 g, 3.88 mmol), *N*-methylmorpholine (0.645 mL, 5.82 mmol), 5 mL anhydrous CH_2Cl_2, and the resulting mixture is stirred at room temperature overnight. The solution is evaporated to dryness under reduced pressure. The residue is redissolved in 8 mL CH_3CN and then applied to a reverse phase HPLC column (C_{18}, 10-95% CH_3CN/ 0.1% TFA water gradient) to give the desired product (**C13**) as a white powder (110 mg, 60% yield): ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.62 (d, J = 5.0Hz, 2H), 7.10 (d, J = 5.0Hz, 2H), 6.80 (s, 2H), 4.74 (s, 1H), 3.72 (s, 2H), 2.89 (t, J = 3.9Hz, 2H), 2.81 (t, J = 3.9Hz, 2H), 1.43 (s, 18H), 0.41 (s, 6H); Retention time in RP-HPLC (C_{18}, 30-95% CH_3CN in 0.1% TFA/H_2O over 7 min) is 4.54; Calculated mass for $C_{27}H_{39}O_6Si$ $(M+H)^+$ 487.3, found by LC-MS 487.3; Elemental analysis for $C_{27}H_{38}O_6Si$ calcd: C, 66.63; H, 7.87; O, 19.73; Si, 5.77; found: C, 66.23; H, 7.48; N, 0.15.

*4-(((3,5-Di-tert-butyl-4-hydroxyphenoxy)methyl)dimethylsilyl)phenyl 2-(dimethylamino)acetate (**C14**)*

To a 15-mL round bottom flask is added 4-(((4-phenol)dimethylsilyl)methoxy)-2,6-di-*tert*-butylphenol (25) (0.200 g, 0.52 mmol), *N,N*-dimethylglycine HCl salt (0.109 g, 0.78 mmol), PS-carbodiimide (2.1 mmol/g, 0.37 g, 0.78 mmol), *N*-methylmorpholine (0.087 mL, 0.78 mmol), DMAP (6.5 mg, 0.052 mmol), 10 mL anhydrous CH_2Cl_2, and the resulting mixture is stirred at room temperature overnight. The resin is filtered off and the solution is evaporated to dryness under reduced pressure. The residue is redissolved in 8 mL CH_3CN and then applied to a reverse phase HPLC column (C_{18}, 10-95% CH_3CN/ 0.1% TFA water gradient) to give the desired product (**C14**) as a white powder (205 mg, 76% yield): ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.66 (d, J = 5.0Hz, 2H), 7.13 (d, J = 5.0Hz, 2H), 6.79 (s, 2H), 4.73 (s, b, 1H), 4.18 (s, 2H), 3.72 (s, 2H), 3.05 (s, 6H), 1.43 (s, 18H), 0.42 (s, 6H); Retention time in RP-HPLC (C_{18}, 30-95% CH_3CN in 0.1% TFA/H_2O over 7 min) is 3.94; Calculated mass for $C_{27}H_{42}O_4Si$ $(M+H)^+$ 472.3, found by LC-MS 472.3; Elemental analysis for $C_{29}H_{42}F_3NO_6Si$ (M+TFA) calcd: C, 59.47; H, 7.23; F, 9.73; N, 2.39; O, 16.39; Si, 4.79; found: C, 58.46; H, 6.30; N, 2.42.

*4-(((3,5-Di-tert-butyl-4-hydroxyphenoxy)methyl)dimethylsilyl)phenyl 4-methyl piperazine-1-carboxylate (**C15**)*

To a 10-mL round bottom flask is added 4-(((4-phenol)dimethylsilyl)methoxy)-2,6-di-*tert*-butylphenol (25) (0.250 g, 0.65 mmol), *p*-nitrophenol chloroformate (0.203 g, 0.97 mmol), *N*-methylmorpholine (0.216 mL, 1.95 mmol), 5 mL anhydrous CH_2Cl_2, and the resulting mixture is stirred at room temperature for 3 hours. 1-Methylpiperazine (0.22 mL, 1.95 mmol) is subsequently added and the stirring continued overnight. The reaction mixture is evaporated to dryness under reduced pressure. The residue is redissolved in 8 mL CH_3CN and applied to a reverse phase HPLC column (C_{18}, 10-95% CH_3CN/ 0.1% TFA water gradient) to give the desired product (**C15**) as a white fluffy powder (211 mg, 64% yield): ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.62 (d, J = 5.0Hz, 2H), 7.10 (d, J = 5.0Hz, 2H), 6.90 (s, 2H), 4.72 (s, b, 1H), 4.41 (s, b, 2H), 3.71 (s, 2H), 2.92 (s, 3H), 2.88 (s, b, 2H), 2.63 (s, b, 4H), 1.43 (s, 18H), 0.41 (s, 6H); Retention time in RP-HPLC (C_{18}, 30-95% CH_3CN in 0.1% TFA/H_2O over 7 min) is 4.04; Calculated mass for $C_{29}H_{45}N_2O_4Si$ $(M+H)^+$ 513.3, found by LC-MS 513.3.; Elemental analysis for $C_{31}H_{45}F_3N_2O_6Si$ (M+TFA) calcd: C, 59.40; H, 7.24; F, 9.09; N, 4.47; O, 15.32; Si, 4.48; found: C, 58.25; H, 6.67; N, 4.57.

*Methyl 2-(4-((3,5-di-tert-butyl-4-hydroxyphenoxy)dimethylsilyl)phenoxy)acetate (**C16**)*

To a 15-mL round bottom flask is added 4-(((4-phenol)dimethylsilyl)methoxy)-2,6-di-*tert*-butylphenol (25) (0.120 g, 0.31 mmol), methyl bromoacetate (0.60 mL, 0.62 mmol), Cs_2CO_3 (0.202 g, 0.62 mmol), 5 mL anhydrous CH_3CN, and the resulting mixture is stirred at room temperature overnight. The solution is evaporated to dryness under reduced pressure, and the residue is applied to a silica gel column eluted with hexanes first followed by 5% EtOAc/hexanes to give the desired product (**C16**) as a white powder (87 mg, 61% yield): ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.54 (d, J = 5.1Hz, 2H), 6.92 (d, J = 5.1Hz, 2H), 6.80 (s, 2H), 4.72 (s, 1H), 4.75 (s, 2H), 3.81 (s, 3H), 3.69 (s, 2H), 1.42 (s, 18H), 0.40 (s, 6H); Retention time in RP-HPLC (C_{18}, 30-95% CH_3CN in 0.1% TFA/H_2O over 7 min) is 4.82; Calculated mass for $C_{26}H_{39}O_5Si$ $(M+H)^+$ 459.3, found by LC-MS 459.3; Elemental analysis for $C_{26}H_{38}O_5Si$ calcd: C, 68.08; H, 8.35; O, 17.44; Si, 6.12; found: C, 67.70; H, 8.04; N, 0.11.

Isopropyl 2-(4-((3,5-di-tert-butyl-4-hydroxyphenoxy)dimethylsilyl)phenoxy)-2-methylpropanoate (C17)

To a 5-mL reaction vial is added 4-(((4-phenol)dimethylsilyl)methoxy)-2,6-di-*tert*-butylphenol (25) (0.220 g, 0.57 mmol), isopropyl 2-bromo-2-methylpropanoate (1.0 mL, 5.65 mmol), Cs_2CO_3 (0.375 g, 1.14 mmol), and the vial is capped and the resulting mixture is heated to 145°C overnight. After cooling down to room temperature, the solution is extracted with 50 mL EtOAc, washed with saturated NH_4Cl, dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. The residue is applied to a silica gel column eluted with 2% EtOAc/hexanes first followed by 5% EtOAc/hexanes to give the desired product (**C17**) as a slightly yellow oil (172 mg, 59% yield): ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.46 (d, J = 5.0Hz, 2H), 6.83 (d, J = 5.0Hz, 2H), 6.80 (s, 2H), 5.08 (p, J = 3.8Hz, 1H), 4.72 (s, 1H), 3.68 (s, 2H), 1.60 (s, 6H), 1.43 (s, 18H), 1.21 (d, J = 3.8Hz, 6H), 0.38 (s, 6H); Retention time in RP-HPLC (C_{18}, 5-100% CH_3CN in 0.1% TFA/H_2O over 12 min) is 11.20; Calculated mass for $C_{30}H_{47}O_5Si$ $(M+H)^+$ 515.3, found by LC-MS 515.3; Elemental analysis for $C_{30}H_{48}O_6Si$ ($M+H_2O$) calcd: C, 67.63; H, 9.08; O, 18.02; Si, 5.27; found: C, 66.22; H, 7.28; N, 0.34.

The following compounds of the invention, and similar compounds, may be prepared according to **Scheme 13**.

4-(((4-(2-(2-methoxyethoxy)ethoxy)phenyl)dimethylsilyl)methoxy)-2,6-di-tert-butylphenol (C18)

To a 10-mL vial is added 4-(((4-phenol)dimethylsilyl)methoxy)-2,6-di-*tert*-butylphenol (25) (0.33 g, 0.85 mmol), 2-(2-methoxyethoxy)ethyl tosylate (1.16 g, 4.25 mmol), Cs_2CO_3 (0.277 g, 0.85 mmol), 2 mL anhydrous DMF, and the resulting mixture is capped and stirred at 60°C for 2 hours. The 50 mL saturated NH_4Cl solution is added and the mixture is extracted with 75 mL EtOAc. The organic layer is separated, washed with brine, and dried over anhydrous Na_2SO_4. The solution is then evaporated to dryness under reduced pressure, and the residue is applied to a silica gel column eluted with by 10% EtOAc/hexanes first followed by 20% EtOAc/hexanes to give the desired product (**C18**) as a white crystaline solid (251 mg, 61% yield): ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.52 (d, J = 4.1 Hz, 2H), 6.94 (d, J = 4.1Hz, 2H), 6.80 (s, 2H), 4.72 (s, 1H), 4.16 (t, J = 3.0Hz, 2H), 3.87 (t, J = 3.0Hz, 2H),

3.73 (t, J = 2.8Hz, 2H), 3.70 (s, 2H), 3.58 (t, J = 2.8Hz, 2H), 3.39 (s, 3H), 1.43 (s, 18H), 0.39 (s, 6H); Retention time in RP-HPLC (C_{18}, 30-95% CH_3CN in 0.1% TFA/H_2O over 5 min) is 4.29; Calculated mass for $C_{28}H_{45}O_5Si$ $(M+H)^+$ 489.3, found by LC-MS 489.3; Elemental analysis for $C_{28}H_{44}O_5Si$ calcd: C, 68.81; H, 9.07; O, 16.37; Si, 5.75; found: C, 67.50; H, 8.92.

E. Preparation of N-Methylbenzylamide Derivatives:

The following compounds of the invention, and similar compounds, may be prepared according to **Scheme 14.**

2-(2-methoxyethoxy)-N-(4-(((3,5-di-tert-butyl-4-hydroxyphenoxy)methyl) dimethylsilyl)benzyl)-N-methylacetamide (C20)

A solution of HOBt (35 mg, 0.25 mmol), HBTU (98 mg, 0.25 mmol), DIEA (0.090 mL, 0.516 mmol), 2-(2-methoxyethoxy)acetic acid (35 mg, 26 mmol) and DMF (4 mL) are added to a solution of 18 (0.035 g, 0.086 mmol) in DMF (1 mL). The homogeneous solution is stirred overnight and quenched with water (50 mL). The organic materials are extracted with EtOAc (3x20 mL) and washed with water (2x50 mL), brine (50 mL), dried (anh. Na_2SO_4), filtered and evaporated. The product is purified by silica gel column using 30-50% EtOAc/hexanes as eluents. The pure product (**C20**) is obtained as pale yellow oil in 78% (0.035 gm) yield.

^{1}H NMR: ($CDCl_3$, 300MHz) (most of the NMR signals are split into two identical sets having intensity ratio of 1:1.4) δ; 7.59 and 7.56 (d, J = 4.60 Hz, 2H), 7.24 and 7.18 (d, J = 4.70 Hz, 2H), 6.79 (s, 2H), 4.73 (s, 1H), 4.58 and 4.49 (s, 2H), 4.27 and 4.26 (s, 2H), 3.70 (m, 3H), 3.60 (m, 2H), 3.59 (m, 1H), 3.38 and 3.33 (s, 3H), 2.93 and 2.91 (s, 3H), 1.42 (s, 18H), 0.41 (s, 6H);

Analytical HPLC: (C_{18}20-90% CH_3CN in 0.1%TFA/H_2O over 15 min) R_t =10.91;

LCMS: Calculated for $C_{30}H_{47}NO_5Si$ = 529.32; Found = 530.3 $[M+H]^+$

2-(2-(2-methoxyethoxy)ethoxy)-N-(4-(((3,5-di-tert-butyl-4-hydroxyphenoxy) methyl)dimethylsilyl)benzyl)-N-methylacetamide (C19)

Following the same protocol as described for the synthesis of **C20**, the reaction between 18 (0.035 g, 0.086 mmol), HOBt (35 mg, 0.25 mmol), HBTU (98 mg, 0.25 mmol), DIEA (0.090 mL, 0.516 mmol), and 2-[2-(2-methoxy ethoxy)

ethoxy]acetic acid (46 mg, 26 mmol) in DMF (5 mL) gave the desired amide (**C19**) as a pale yellow oil in 74% yield (0.036 g).

^{1}H NMR ($CDCl_3$, 300MHz) (most of the NMR signals are split into two identical sets having intensity ratio of 1:1.4) δ; 7.59 and 7.56 (d, J = 4.60 Hz, 2H), 7.24 and 7.18 (d, J = 4.70 Hz, 2H), 6.79 (s, 2H), 4.73 (s, 1H), 4.58 and 4.55 (s, 2H), 4.27 and 4.26 (s, 2H), 3.76 (m, 1H), 3.71 (m, 3H), 3.65 (m, 2H), 3.64 (m, 2H), 3.54 (m, 1H), 3.38 and 3.36 (m, 1H), 3.34 (m, 1H), 2.93 and 2.91 (s, 3H), 1.42 (s, 18H), 0.41 (s, 6H);

Analytical HPLC: (C_{18}20-90% CH_3CN in 0.1%TFA/H_2O over 15 min) R_t =10.89;

LCMS: Calculated for $C_{32}H_{51}NO_6Si$ = 573.35; Found = 574.3 $[M+H]^+$

F. Preparation of Sulphonamide Derivatives:

The following compounds of the invention, and similar compounds, may be prepared according to **Scheme 15.**

N-(4-(((3,5-di-tert-butyl-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)-4-methoxy-N-methylbenzenesulphonamide(C21)

To a solution of compound 18 (0.035 g, 0.086 mmol) in dry CH_2Cl_2 (4 mL), Et_3N (0.024 mL, 0.172 mmol) is added and the reaction is cooled to 0°C. A solution of 4-methoxy benzenesulphonyl chloride (0.022 mg, 0.106 mmol) in CH_2Cl_2 (1 mL) is added slowly and the solution is stirred for 6 hrs. All the solvent is removed under vacuum and the residue is dissolved in EtOAc (50 mL) and treated with an aqueous sat. NH_4Cl (50 mL) solution. The organic layer is separated and washed with water (2x50 mL), brine (50 mL), dried (anh. Na_2SO_4), filtered and evaporated. The product is purified by silica gel column using 20-50% EtOAc/Hexanes as eluents. The pure product (**C21**) is obtained as colorless solid in 70% (0.035 gm) yield.

^{1}H NMR($CDCl_3$, 300MHz) δ; ($CDCl_3$, 300MHz) δ; 7.78 (d, J = 6 Hz, 2H), 7.56 (d, J = 4.81 Hz, 2H), 7.31 (d, J = 4.8 Hz, 2H), 7.03 (d, J = 5.7 Hz, 2H), 6.79 (s, 2H), 4.73 (s, 1H), 4.12 (s, 2H), 3.89 (s, 3H), 3.71 (s, 2H), 2.58 (s, 3H), 1.42 (s, 18H), 0.41 (s, 6H);

Analytical HPLC: (C_{18}20-90% CH_3CN in 0.1%TFA/H_2O over 15 min) R_t =12.73;

LCMS: Calculated for $C_{32}H_{45}NO_5SSi$ = 583.3; Found = 584.3 $[M+H]^+$

N-(4-(((3,5-di-tert-butyl-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)-2,4-dichloro-N-methyl benzenesulphonamide(C22)

Following the same protocol as described for the synthesis of **C21**, the reaction between 18 (0.035 g, 0.086 mmol), Et_3N (0.024 mL, 0.172 mmol), 2,4-dichloro benzenesulphoyl chloride (0.026 mg, 0.106 mmol) and CH_2Cl_2 (5 mL) gave the desired sulphonamide (**C22**) as semisolid material in 94% yield (0.050 g).

^{1}H NMR δ; 8.04 (d, J = 5.1 Hz, 1H), 7.56 (d, J = 4.81 Hz, 2H), 7.55 (s, 1H), 7.38 (m, 1H), 7.34 (m, 2H), 6.79 (s, 2H), 4.73 (s, 1H), 4.40 (s, 2H), 3.72 (s, 2H), 2.76 (s, 3H), 1.42 (s, 18H), 0.41 (s, 6H);

Analytical HPLC: (C_{18}40-90% CH_3CN in 0.1%TFA/H_2O over 15 min) R_t =11.76;

LCMS: Calculated for $C_{31}H_{41}Cl_2NO_4SSi$ = 621.19; Found = 622.3 $[M+H]^+$

N-(4-(((3,5-di-tert-butyl-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)-4-fluoro-N-methyl benzenesulphonamide(C23)

Following the same protocol as described for the synthesis of XXI, the reaction between 18 (0.035 g, 0.086 mmol), Et_3N (0.024 mL, 0.172 mmol), 4-fluoro benzenesulphoyl chloride (0.020 mg, 0.106 mmol) and CH_2Cl_2 (5 mL) gave the desired sulphonamide (**C23**) as colorless solid in 62% yield (0.030 g).

^{1}H NMR δ; ($CDCl_3$, 300MHz) δ; 7.58 (d, J = 6.0 Hz, 2H), 7.30 (d, J = 4.5 Hz, 2H), 7.23 (m, 4H), 6.79 (s, 2H), 4.73 (s, 1H), 4.15 (s, 2H), 3.71 (s, 2H), 2.60 (s, 3H), 1.42 (s, 18H), 0.41 (s, 6H);

Analytical HPLC: (C_{18}20-90% CH_3CN in 0.1%TFA/H_2O over 15 min) R_t =12.45;

LCMS: Calculated for $C_{31}H_{42}FNO_4SSi$ = 571.26; Found = 572.3 $[M+H]^+$

N-(4-(((3,5-di-tert-butyl-4-hydroxyphenoxy)methyl)dimethylsilyl)benzyl)-N-methyl methylsulphonamide(C24)

Following the same protocol as described for the synthesis of XXI, the reaction between 18 (0.035 g, 0.086 mmol), Et_3N (0.024 mL, 0.172 mmol), methanesulphonyl chloride (0.0085 mg, 0.106 mmol) and CH_2Cl_2 (5 mL) gave the desired sulphonamide (**XXIV**) as pale yellow oil in 48% yield (0.020 g).

^{1}H NMR($CDCl_3$, 300MHz) (most of the NMR signals are split into two identical sets having intensity ratio of 1:1.4) δ; 7.61 and 7.56 (d, J = 4.60 Hz, 2H), 7.22 and 7.04 (d, J = 4.70 Hz, 2H), 6.79 (s, 2H), 4.73 and 4.72 (s, 1H), 4.58 and 4.52 (s, 2H), 3.72 and 3.71 (s, 2H), 2.95 and 2.93 (s, 3H), 2.18 and 2.15 (s, 3H), 1.42 (s, 18H), 0.41 (s, 6H);

Analytical HPLC: (C_{18}12-90% CH_3CN in 0.1%TFA/H_2O over 15 min) R_t =12.46;

LCMS: Calculated for $C_{26}H_{41}NO_4SSi$ = 491.25; Found = 492.3 $[M+H]^+$

All publications and patent applications cited herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Although certain embodiments have been described in detail above, those having ordinary skill in the art will clearly understand that many modifications are possible in the embodiments without departing from the teachings thereof. All such modifications are intended to be encompassed within the claimed invention.